

pharmacologic and mechanical aspects of direct medication of the lung in man. Penicillin was chosen for this study for several reasons. It is, at present, the most frequently used agent in this form of therapy. It is free from serious toxic side reactions; it is not inactivated in the presence of pus; it is fairly stable in body fluids at freezing temperatures, and its assay in these fluids, although cumbersome, is readily accomplished by a trained bacteriologist.

The various factors requiring study are: (1) the pharmacodynamics of absorption and excretion following intratracheal and aerosol administration as contrasted to parenteral administration; (2) the action, if any, of various vehicles, other than saline, on absorption; (3) the effect of suppuration of the lung on the absorption mechanism; and lastly, (4) the relative efficiency of various methods of aerosolizing therapeutic agents. This report deals with the pharmacodynamics of absorption and excretion from the normal human lung.

Absorption from normal alveoli involves a more complex mechanism than absorption from muscle or subcutaneous tissue. Fluids must pass through the epithelium-lined wall of the alveoli and then cross the endothelium-lined capillaries into the blood stream. An alternative route is presented by the endothelium-lined lymphatics with which the alveoli are richly supplied. It is well known that fluids are absorbed from the bronchioles, bronchi and even the trachea. The relatively small surface area of the tracheobronchial tree as compared to that of the alveoli, makes absorption from the tracheobronchial mucosa quantitatively unimportant. As previously mentioned, the literature contains few references to the manner in which molecules of various sizes are absorbed from the lungs. The only studies recorded have been made in relation to war gas poisoning, pulmonary edema, and in Drinker's fundamental work on the lymphatic drainage of the lungs. Winternitz and Smith,<sup>6</sup> after the First World War, demonstrated that physiologic saline was rapidly absorbed when injected into the trachea of anesthetized dogs. Phenolsulfonphthalein, similarly administered, appeared almost immediately in the urine. Courtice and Phipps,<sup>7</sup> more recently in the course of studies with phosgene poisoning, administered water, physiologic saline and serum endotracheally to anesthetized rabbits and dogs and collected the flow from the right lymphatic duct in the latter. They were able to calculate the amount of fluid absorbed from the lungs by comparing the normal heart/lung weight ratio to that found after sacrificing the experimental animals at various intervals. Figure 1, taken from their article, illustrates their findings: 80 per cent of the water and 23 per cent of the saline were absorbed within the first hour. Serum absorbed very slowly, about four days being required for complete removal of all the material. The lymph flow was not appreciably increased above the normal; thus very little of this fluid was absorbed by the lymphatics. The ease with which water and molecules the size of sodium chloride and even phenolsulfonphthalein are absorbed from the lung is now evident. Drinker<sup>8</sup> in similarly arranged experiments,

A rational approach to the study of absorption and excretion of penicillin administered by the aerosol route necessitates an accurate determination of the amount of the active agent which actually reaches the pulmonary epithelium. It would seem, at first, that this amount might be calculated by comparing the total urinary excretion of the intramuscularly administered penicillin to that excreted following aerosol administration. If no penicillin were inactivated or detoxified within the body, such a comparison would hold. However, it is well established that only 40 to 60 per cent of parenterally administered penicillin can be recovered from the urine.<sup>10, 11, 12</sup> Moreover, the processes by which the balance of the biotherapeutic agent is detoxified or inactivated and the organs involved in this mechanism have not been established. Penicillin given intravenously to patients with complete renal shutdown disappears from the blood at a logarithmic rate with a half-life of about two hours.<sup>13</sup> Any interference with urinary excretion, due to renal insufficiency or drugs competing with penicillin for tubular excretion, such as diodrast, p-aminohippuric acid, caronamide, and others, may reduce the percentage of excreted penicillin in the urine to 30 per cent or less.<sup>12, 14, 15, 16</sup> Thus it appears that the amount of penicillin excreted is inversely related to the time of exposure within the body as a whole.

It also seems apparent that the capacity of the specific organ (the site of administration) to inactivate penicillin will inversely affect the urinary excretion. The influence of muscle or gastrointestinal mucosa on penicillin has been well established, but the effect which the pulmonary epithelium exerts is not known. It would, therefore, appear desirable to administer the drug into the tracheobronchial tree in such a fashion that no losses occur. If the percentage of urinary excretion under such conditions were known, a comparison with the excretion of aerosolized penicillin would be valid, and the effectiveness of this latter mode of administration could be calculated. Large losses with inhalational administration may be expected, largely due to technical difficulties. Loss in the apparatus and in the mouth can be relatively easily determined, as described elsewhere.<sup>17</sup> However, it is not so easy to determine the amount of active agent lost to the outside air. This loss may be expected to be the largest due to the following: (1) part of the inspired air (the dead space air) does not reach the alveoli and, therefore, most of the fluid particles are not removed; (2) the smallest droplets may enter the alveoli and leave them again on expiration without having been deposited; and (3) prevention of some loss to the outside air during aerosolization is impossible. A quantitative basis for the study of absorption and excretion following pulmonary administration requires a method by which the above mentioned losses are eliminated. We therefore elected to administer penicillin solution directly into the tracheobronchial tree by endotracheal catheter.

## METHODS

The procedure used for endotracheal catheterization was identical to that used by the Thoracic Surgical Service to instill radio-opaque oil for



refrigerated for no longer than 24 hours. Storage for longer periods of time caused a loss in penicillin activity detectable by this method. Urines were not buffered since it has been shown that penicillin excreted in the urine is more stable than commercial penicillin and will tolerate a pH as low as 2.2 for long periods of time.<sup>23</sup> This method of assay is no more accurate than other methods of biological assay involving serial dilution. Each numerically expressed level signified that the specimen contains about half as much active substance as would be needed for a positive reaction in the next tube. In order not to give a false impression of accuracy, we have used the values of 0.16, 0.08, 0.04, 0.02, etc., rather than the values obtained by serially dividing 20 (the number of units per c.c. of standard) by 2, namely 10 . . . 2.5 . . . 0.625 . . . 0.156, 0.078, 0.039, 0.019.

## RESULTS

A total of 297 specimens were assayed, of which 167 were bloods, 108 urines and 22 apparatus and mouth rinses. Ten volunteers received 100,000 units of penicillin intramuscularly in 1 c.c. of saline (chart 1). The results

CHART I

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline (K-Salt) Penicillin (C.S.C.) in 1 c.c. Saline by the Intramuscular Route in 10 Subjects

	Blood							Urinary Excretion				
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.
No. 1	1.25	.63	.08	—	.02	—	—	24,960	5,070	—	390	27
No. 2	.16	.16	.08	—	—	—	—	—	—	—	—	—
No. 3	.31	.63	.31	.08	.04	.02	.00	4,368	10,250	13,750	2,340	300
No. 4	.63	.31	.08	.04	.00	.00	.00	72,500	10,750	4,750	796	900
No. 5	1.25	.63	.31	.08	.04	.00	.00	18,750	4,750	12,250	—	250
No. 6	2.50	1.25	.16	.08	.00	.00	.00	22,500	6,250	14,750	—	1,875
No. 7	1.25	.63	.23	.08	.02	—	—	17,750	3,750	4,368	725	204
No. 8	.63	.63	.16	.08	.02	.02	.00	31,500	12,000	2,934	897	31
No. 9	1.25	.63	.16	.04	.00	.00	.00	35,500	11,500	1,248	117	24
No. 10	1.25	.63	.31	.16	.04	.02	.00	35,250	19,375	4,992	702	689
Average	1.05	.61	.19	.07	.02	.01	.00	29,231	9,299	7,380	852	478
								(Total—47,240)				

varied somewhat from one individual to another but, on the whole, were fairly uniform. The highest blood levels occurred one-half hour after administration and the average level, at that time, was about 1 unit per c.c. of serum. A rapid decline followed and levels generally considered to be significant were maintained for three hours only. There was no evidence of any penicillin activity at the end of six hours in any of the blood specimens. The urinary excretion paralleled these blood levels very closely. An average of 29,231 units was excreted during the first hour with a rapid decline thereafter. The total average excretion, 47,240 units or 47.24 per cent, was slightly below the figure generally reported in the literature.

maintained for twice as long as with intramuscular administration (six hours). Urinary excretion correspondingly was much lower at one hour (8,060 units) and fell off less rapidly; almost an equal hourly amount was excreted from the second to the sixth hour. The total excretion of 15.9 per cent was roughly one third that obtained following intramuscular administration. These serum levels and urinary excretions are compared in figure 2.

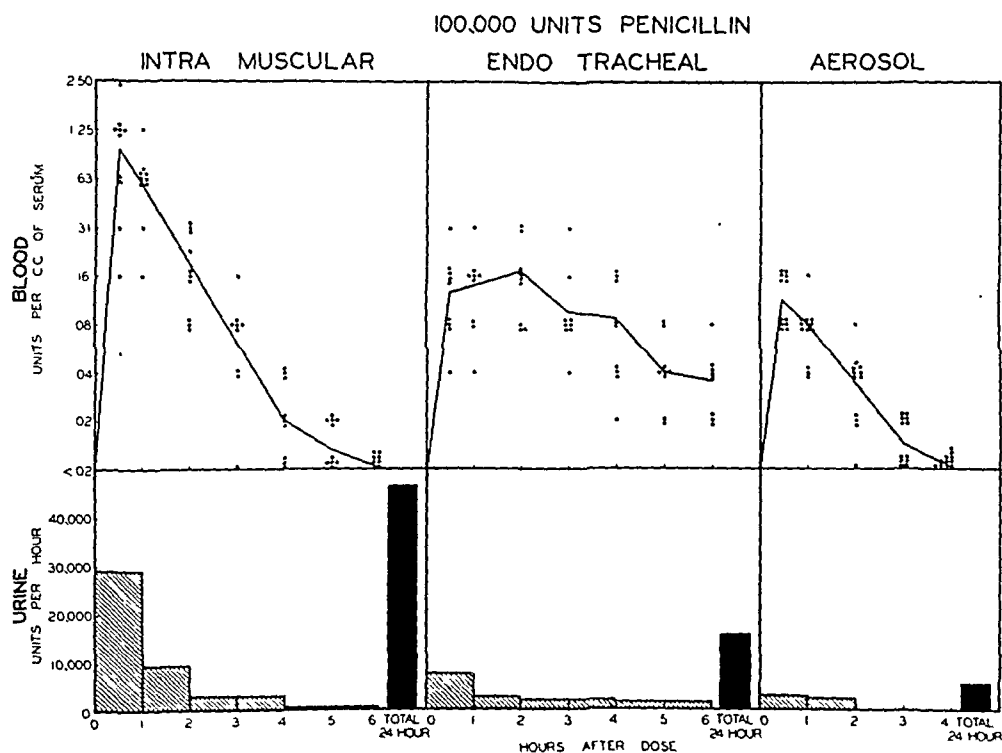


FIG. 2. Blood levels and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by various routes in normal male subjects.

Twelve patients received 100,000 units of penicillin in 1 c.c. of saline by aerosolization with the nebulizer-rebreathing bag apparatus (chart 3). The average blood level at one-half hour (0.12 unit per c.c.) parallels the corresponding level following endotracheal injection. Although the average at two hours was 0.04 unit per c.c., five of the 12 serums showed less than this therapeutically effective amount. No significant levels were encountered after two hours. Thus, although the aerosol curve reaches almost the same peak as the endotracheal curve, it drops off more quickly. Urinary excretion corresponds very closely. The total excretion averaged 5.46 per cent, approximately one third of the endotracheal excretion. These relationships are illustrated in figure 2.

### DISCUSSION

On comparing the parenteral and endotracheal blood level curves, several facts become evident. Absorption from the alveoli is much slower than from

blood levels by this route, injections are necessary only one-half as often as a similar dose given parenterally. Several methods of endobronchial administration of penicillin have been previously suggested. Kay and Meade<sup>27</sup> injected 250 to 10,000 units in 3.0 to 5.0 c.c. of saline by indirect laryngoscopy through a laryngeal cannula, without anesthesia, and reported favorable results in ulcerative tracheobronchitis, minimal bronchiectasis, and in preoperative treatment. Moore and Thompson<sup>28</sup> treated severe bronchiectasis with bronchial lavage and intratracheal penicillin and sulfathiazole under nupercaine anesthesia. Bobrowitz et al.<sup>29</sup> gave six bronchiectatic patients 50,000 to 250,000 units a day by the supraglottic method of instillation following cocaineization; they recorded rapid and satisfactory symptomatic improvement. Romansky<sup>30</sup> treated 12 cases of pulmonary suppurative disease with endotracheal penicillin suspended in iodized heavy oil.

We do not propose this form of treatment as a routine measure for several reasons. In order to obtain penicillin levels comparable to the ones we obtained, it is necessary to abolish the cough reflex by topical anesthesia. This not only introduces the well known hazards of topical anesthesia, but also violates an important therapeutic principle in the management of bronchopulmonary disease—maintenance of adequate cough reflex. This would be highly undesirable in the very diseases where primary application of penicillin to the tracheobronchial tree is indicated. Finally the technic of endotracheal intubation is more difficult and not as well tolerated by the patient as aerosolization.

In another study, dealing with absorption of penicillin in chronic suppurative pulmonary disease, we have consistently shown that parenterally administered penicillin does not reach the purulent sputum.<sup>31</sup> It has been the impression for some time that parenteral therapy will not penetrate the walled-off purulent cavity but will improve a surrounding pneumonitis.<sup>27, 28, 29</sup> Since the primary aim of penicillin administered directly to the lung is the production of high local concentrations, the nebulizer is the most practical tool by which the therapeutic agent can be placed at the site of the pathologic process. Endotracheal manipulation and topical anesthesia are not necessary. Most patients are easily taught to use the aerosol apparatus themselves in the hospital or at home. Furthermore, we have shown elsewhere that the amount of penicillin deposited in the lung, as evidenced by the penicillin excreted in the sputum, compares favorably with the endotracheal method. Our<sup>31</sup> experiences on the Inhalational Therapy Service and the Thoracic Surgical Service do suggest, however, that in certain special cases biotherapeutic agents may be given to great advantage by the endotracheal route. Such is the case when endotracheal intubation is necessary, primarily for other reasons, as at time of bronchoscopy or bronchography, during the course of endotracheal aspiration therapy following thoracic surgery, or in the treatment of acute atelectasis. Our experiences also suggest that when a rapid and striking reduction of sputum is necessary prior to surgery for sup-

solution is actually absorbed by the lungs, one sixth is lost within the apparatus and the oropharynx and almost one-half is lost into the air.

### SUMMARY

1. Intratracheal administration of penicillin in saline solution in normal, anesthetized volunteers revealed that the penicillin molecule is readily absorbed into the blood stream from the alveoli. This absorption is notably slower than that following parenteral administration.

2. Blood levels following intratracheal instillation do not reach the early high peaks seen on intramuscular administration but therapeutically significant blood levels are maintained for twice as long a period of time. The average urinary excretion is 15.9 per cent, or about one third of that following parenteral administration. This suggests that the lung may act as a *depot* from which penicillin may be slowly released.

3. Intratracheal administration is suggested as a practical and advantageous method of therapy under certain, special circumstances.

4. Aerosolized penicillin solution results in early blood levels nearly as high as those obtained by endotracheal administration, but therapeutic levels are maintained for only one third as long a period of time.

5. Following aerosolization, 5.5 per cent of the administered penicillin is excreted into the urine; 10.2 per cent is lost within the apparatus, 8 per cent is lost in the oropharynx and 47.5 per cent is lost on expiration and other losses into the air. Thus one third of the aerosolized penicillin solution actually reaches the lung.

### BIBLIOGRAPHY

1. GRAESER, J. B., and ROWE, A. H.: Inhalation of epinephrine for the relief of asthmatic symptoms, *Jr. Allergy*, 1935, vi, 415-420.
2. BRYSON, V., SANSOME, E., and LASKIN, S.: Aerosolization of penicillin solutions, *Science*, 1944, c, 33-35.
3. BARACH, A. L., SILBERSTEIN, F. H., OPPENHEIMER, E. T., HUNTER, T., and SOROKA, M.: Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis and lung abscess: preliminary report, *Ann. Int. Med.*, 1945, xxii, 485.
4. SEGAL, M. S., and RYDER, C. M.: Penicillin aerosolization in the treatment of serious respiratory infections. A preliminary report, *New England Jr. Med.*, 1945, ccxxxiii, 747.
5. RICHARDS, D. W., BARACH, A. L., and CROMWELL, H. A.: Use of vaporized bronchodilator solutions in asthma and emphysema. A continuous inhalation method for severe asthmatic states, *Am. Jr. Med. Sci.*, 1940, cxcix, 225-232.
6. WINTERNITZ, M. C., and SMITH, G. H.: Preliminary studies in intratracheal therapy, collected studies on the pathology of war gas poisoning, 1920, Yale University Press, New Haven.
7. COURTICE, F. C., and PHIPPS, P. J.: The absorption of fluids from the lungs, *Jr. Physiol.*, 1946, cv, 186-190.
8. DRINKER, C. K., and HARDENBERGH, E.: Absorption from the pulmonary alveoli, *Jr. Exper. Med.*, 1947, lxxxvi, 7-18.
9. RAWSON, R. A.: The binding of T-1824 and structurally related diazo dyes by the plasma proteins, *Am. Jr. Physiol.*, 1943, cxxxviii, 708-717.

# THE HEREDITY OF GOUT AND ITS RELATIONSHIP TO FAMILIAL HYPERURICEMIA \*

By ROBERT M. STECHER, M.D., F.A.C.P., A. H. HERSH, Ph.D., and  
WALTER M. SOLOMON, M.D., F.A.C.P., *Cleveland, Ohio*

DESPITE the fact that gout has long been recognized as a hereditary disease and that much study has been devoted to this phase of the problem, the exact pattern of inheritance has not been clearly identified. It seemed likely that a broader concept of the disease and the application of modern methods of genetic investigation to readily available data might add much to our understanding of the disease. The present study was undertaken in the hope that these potentialities might be realized.

The most striking features of gout have always been associated with the joint phenomena. Characteristically these consist of a series of sudden, acute, painful attacks of arthritis involving with decreasing frequency the joints of a big toe, the feet, the knees and the hands. The joints may become affected overnight and are greatly swollen, very red, markedly tender and hot. There is often fever and leukocytosis. The attacks subside spontaneously in days to months and complete recovery is the rule. Only as a result of repeated attacks and after many years does chronic joint damage with deformity occur. The deposition of uric acid crystals as tophi in the skin about the ears, or in bones about the joints and resulting in punched-out areas seen by roentgen-ray, are the pathognomonic lesions of the disease. They appear only late in the disease, if at all, and they escape detection entirely in many victims. Because the joint manifestations of gout characteristically occur only in middle or later life and because they are often atypical and cannot be correctly identified, many affected members of the gouty family are not recognized and the genetic pattern is rarely complete.

Gouty patients have an abnormally high level of uric acid in the blood, one manifestation of the faulty uric acid metabolism which is characteristic of the disease. Hyperuricemia is present whether the patient is having gouty attacks or not and this abnormality has been observed in patients before they developed clinical gout. A substantial proportion of the near relatives of gouty people have been found to have hyperuricemia. This suggested that the genetic pattern and the mechanism of inheritance of familial hyperuricemia might be recognized and that analysis of this trait could yield valuable information about the heredity of gout. The present study, therefore, is one of the genetics of familial hyperuricemia and for this purpose familial hyperuricemia is considered to have exactly the same significance as clinical gout.

\* Received for publication April 21, 1947.

From the Department of Medicine, School of Medicine at City Hospital and the Department of Biology, Western Reserve University.

TABLE I  
Serum Uric Acids  
1272 determinations on 1,162 individuals

	Number of Individuals	Number of Determinations	Determinations below 6.5 mg.	Determinations 6.5 mg. or over	Average
A. Gouty families					
1. Index cases	41	77	3	74	8.12
2. Hyperuricemia	17	23	1	22	7.37
3. Normal relatives	120	124	123	1	
4. Spouses of gout	23	24	22	2	
Total	201	248	149	99	
B. General population					
5. Normal kidney function	878	927	893	34	
6. Nitrogen retention	83	97	72	25	
Total	961	1,024	965	59	
Grand total	1,162	1,272	1,114	158	

stances, 94 per cent of 177 determinations on 21 gouty subjects being over 7 mg. per 100 c.c. Among 100 non-gouty subjects there were only three determinations above 6 mg.

Because of the importance of recognizing a definite level between hyperuricemia and normal it seemed desirable to determine the dividing line to be used in this study from our own experience of 1,272 tests. These included 248 tests on 41 gouty patients and 159 of their relatives or spouses and 1,024 tests done routinely on 961 patients on the medical wards of Cleveland City Hospital, shown in table 1. All determinations used in this study were made by one individual using Benedict's direct method, and read with a Klett Electric Colorimeter on serum separated from clotted blood. Specimens were collected under oil without regard to fasting.

Table 2 shows the distribution of values in various classes of individuals. Examination of this table shows a natural division of high and low levels

TABLE II  
Serum Uric Acid Levels  
Distribution of 1,272 determinations

	0- 1.9	2.0- 2.4	2.5- 2.9	3.0- 3.4	3.5- 3.9	4.0- 4.4	4.5- 4.9	5.0- 5.4	5.5- 5.9	6.0- 6.4	6.5- 6.9	7.0- 7.4	7.5- 7.9	8.0- 8.4	8.5- 8.9	9+
A. Gouty families																
1. Index cases									1	2	8	13	14	12	15	12
2. Hyperuricemia									1	1	7	7	3	3		2
3. Normal relatives			6	11	21	22	16	25	18	4	1					
4. Spouses of gout		1	3	2	2	3	6	2	2	1	1		1			
Total 248		1	9	13	23	25	22	27	21	8	17	20	18	15	15	14
B. General population																
5. Normal kidney function	54	65	106	136	153	162	80	70	42	25	12	5	8	1	2	6
6. Nitrogen retention	2	1	5	7	11	11	12	6	11	6	4	7	3	2	3	6
Total 1,024	56	66	111	143	164	173	92	76	53	31	16	12	11	3	5	12
Grand total 1,272	56	67	120	156	187	198	114	103	74	39	33	32	29	18	20	26

TABLE III  
Pedigrees of 40 Gouty Families

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
1. M. A. male (63) 8.0 8.0		(62) 2.9				(39) 4.4 (38) 5.4 (35) 5.9 (31) 5.9 (27) 4.9 (23) 5.1	(40) 3.9
2. C. B. male (65) 10.8 9.5				(70) 5.2			
3. J. B. male (50) 6.5			(72) 4.2		(41) 2.6		
4. G. C. male (62) 7.8 7.2 7.8 7.3		(58) 5.6				(36) 5.2	(28) 4.6
5. E. C. male (61) 7.6 8.1					(64) 3.7 (62) 4.3 (60) 3.7 (56) 5.1		(38) 5.1
6. D. D. male (70) 8.4 8.8						(48) 4.1 (38) 4.6 (32) 5.8 (25) 7.2	(36) 5.4
7. L. D. male (48) 7.3				(66) 5.4	(51) 7.1		
	8. B. B. female (51) 7.1	(45) 6.0				(12) 4.8	(30) 3.7 (28) 4.8 (26) 4.1 (25) 4.7 (24) 4.5 (22) 4.8 (19) 4.8 (16) 4.3
9. F. D. male (46) 7.0 5.5			(74) 4.4				

TABLE III—*Continued*

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
21. O. K. male (53) 8.9	.	(55) 4.6		(61) 6.1		(14) 4.0	(32) 4.4
22. E. L. male (50) 9.2		(48) 5.2	(81) 4.8	(52) 5.3		(19) 5.7	(17) 4.9
23. A. L. male (62) 8.5 9.2 8.5				(48) 7.5			
24. O. L. male (68) 7.2 8.1		(66) 3.3					(39) 3.0 (34) 3.6
25. S. N. male (43) 6.6 6.3		(40) 2.9	(65) 4.5	(37) 5.6			(13) 4.4
26. J. P. male (58) 7.3 8.4 8.7 10.7			(80) 9.4 8.3	(55) 3.4 (44) 3.4	(49) 3.9 (42) 2.8		
27. J. P. male (66) 7.7 7.2 9.0 7.6				(70) 6.1 (65) 5.6		(42) 5.5 (35) 5.8	(41) 3.7
28. E. S. male (46) 8.5		(44) 4.8	(69) 9.3	(45) 7.0		(19) 5.7	(16) 4.7
	29. Mrs. S. female (69) 6.7 9.3				(71) 6.9 (65) 7.1		
	30. Mrs. B. female (65) 7.1	(80) 4.5				(45) 7.6 (40) 8.1 (38) 5.2	
	31. Mrs. B. female (71) 6.9						(48) 5.3 (31) 5.2



presented in table 3. This shows the age when seen and sex of each index case, the age, sex and relationships of each relative examined and all of the serum uric acid determinations done on the entire group in the course of this study. The spouses are included so that the reader may reconstruct the pedigrees if he wishes. Each secondary index case is a duplication having been shown before in a previous family. Initials are given only for index cases. The relationship is shown by the column, age is given in brackets. The relatives we have considered affected are indicated by underlining.

Of the 44 primary index cases, all had gout, all were male, all had high serum uric acid levels, save three men with undoubted gout, known to have had a high level of whole blood uric acid but who died before this study was started, and whose families were known and available to us. Seventy-seven serum uric acid determinations on these 41 index cases averaged 8.12 mg. per cent. The lowest determinations were 5.5, 6.2 and 6.3 mg. per cent, these three being all that fell below 6.5 mg. each in an individual who had other determinations above this level.

TABLE IV  
Hyperuricemia in Relatives

	Mother	Brother	Sister	Son	Daughter
Number examined	11	23	24	33	45
Number affected	2	4	5	5	0
Proportion affected (%)	18	17	21	15	0

Having the above data available, it seemed desirable to investigate the proportions of involvement among different degrees of relationship. The results are shown in table 4. Because of the known preponderance of gout in males it seems desirable to consider each sex separately. Inquiry was made concerning all the parents. Of 88 parents of 44 primary index cases only 12 were available for examination. These included the mother in 11 families. Twice she was found to have hyperuricemia but never gout. One father (of the index case J. H., family No. 15) examined was thought to have gout clinically but he showed a normal uric acid level twice. One other father was reported to have had gout but he has not been included in our computations. Thus 2 of 12 parents or about 17 per cent of those examined were found to have hyperuricemia. No attempt was made to analyze involvement of parents of the hyperuricemic relatives because they had one involved parent by definition.

Of the primary index cases, 16 had brothers. These 16 men had 23 brothers of whom 4 or 17 per cent had hyperuricemia. Twelve primary index cases had 22 sisters. One other person, the mother of an index case, had hyperuricemia and her 2 sisters had hyperuricemia, one of them gout. Of 24 sisters then, 5 or 21 per cent had hyperuricemia. The incidence of hyperuricemia in the siblings of gouty people is about 20 per cent and there is no significant sex difference.

times. Seventeen of the fathers had gout, two had hyperuricemia. All the mothers had hyperuricemia.

Study of table 5 shows the proportion of involved offspring from various combinations of involved and normal parents. In only one family, No. 15, were both parents involved, the father with gout, the mother with hyperuricemia. The four daughters from this union were normal. There were no sons. In nine families sons were born of gouty fathers and normal mothers (Nos. 38, 1, 14, 18, 4, 21, 22, 28, 17). In two other families the father had hyperuricemia without gout, the mother was normal (Nos. 32, 33). These families had 18 sons and 16 daughters. In only one family of this known combination was an affected son produced (No. 38). In five other families with gouty fathers, but mothers unknown (Nos. 6, 27, 10, 37, and 40), there were nine sons and two daughters with only one son affected (No. 6). There were six families with mothers with hyperuricemia and three normal fathers (Nos. 8, 30, 13) and three fathers untested (Nos. 28, 26, 31). In family 26 reference is to parents of the index case. There were 11 sons in these families of whom six were affected. Four of these families had daughters (Nos. 8, 26, 13, 31), a total of 13, all normal. Both parents of index case No. 15 were normal and both sons, their only children, were affected. In eight other families, the mothers were normal and fathers unknown (Nos. 39, 3, 9, 10, 11, 19, 22, and 25). These eight families will not be discussed because the possibilities of an affected father cannot be excluded.

In six families with gouty fathers (Nos. 34, 24, 20, 36, 25, 5) and another family with hyperuricemic father (No. 16) and the mothers normal or unknown, there was a total of 13 daughters, all normal, but no sons.

It is seen that in every instance where something was known about at least one parent, not a single affected daughter among 48 was found although there were 10 affected of 40 sons. Furthermore, the degree of involvement in the parents was no reliable index as to how they would transmit the abnormality. Two affected parents had only four daughters, all unaffected. Two normal parents with only two sons had both affected. Of 23 families with the father involved but mother normal or unknown there was a total of 27 sons, of whom only one each in two different families was affected. There were 31 daughters in these families, only three of whom were in the two families with affected sons. There were six families with affected mothers and normal or unknown fathers. These families produced 11 sons of whom six were affected. Four of these six families produced affected sons. These four families with six affected sons produced only three daughters. Thus with the father affected, only two of 27, or 8 per cent of the sons were affected. With mothers affected, six of 11, or one-half of the sons were affected. The effect of sex was marked. The apparent immunity of daughters is not so convincing when we realize that only 6 of 21 families having sons and with one parent involved proved that they could transmit hyperuricemia to a son. Six daughters only sprang from these six

TABLE VI—*Continued*

Family	Total Sons	Affected Sons	Total Daughters	Affected Daughters	Fathers	Mothers
Sibships with Affected Sisters						
29	0	0	3	3	Unknown	Unknown
10*	1	1	1	1	Unknown	Unknown
12*	1	1	1	1	Unknown	Unknown
7*	2	1	1	1	Unknown	Unknown
Sibships with Unaffected Sisters Only						
15			4	0	Gout	H.U.A.
34			4	0	Gout	Normal
24			2	0	Gout	Normal
16			2	0	H.U.A.	Normal
36			1	0	Gout	Normal
25			1	0	Gout	Normal
5			1	0	Gout	Unknown
31			2	0	H.U.A.	Unknown

\* Shown in table of Affected Sons.

is known of the parents. According to table 5, there were 24 sibships with at least one affected brother. In eight of these the constitution of one or both parents is known. These 24 sibships had 51 males of whom 29 or 57 per cent were affected. Of the 24 families 15 or 62 per cent had daughters, 26 in number, of whom one each in three sibships was affected (Nos. 10, 12, 7). Another 15 sibships had 23 males, all normal. Each of these families had an affected parent or it would not have been included in the study. Ten of the sibships had 23 females, all normal. Four families had affected sisters, three mentioned above (Nos. 10, 12, 7) and another (29) with three sisters all involved. Eight additional sibships without sons had 17 daughters, all normal.

Involvement of women with hyperuricemia was rare but significant. Of the four sibships with involved women, a total of six women were examined and all found involved. Of four brothers of these women, three were found affected. Nine of the 10 people in these four sibships involving affected women were affected. Only two other affected females were discovered in the entire study, a spouse (No. 15) and a mother (No. 26). Of the eight women with hyperuricemia, only one could possibly be considered to have clinical gout.

Consideration of the data of table 3 and table 5 is sufficient to show that the inheritance of hyperuricemia exhibits certain irregularities. This is emphasized more clearly by an examination of the pedigrees of several of the more significant families. Figure 1 shows in pedigree form the data for families 15 and 16, while figure 2 gives the pedigree for the related families 28, 29, 30, 31, 32 and 33 of table 3.

parents with affected offspring were heterozygous for a dominant gene which acts irregularly in many families. It is clear that a dominant gene which lacks penetrance can resemble a recessive in some pedigrees.

These two pedigrees, taken in conjunction with the other families of table 3, justify the conclusion that the genetic peculiarities of hyperuricemia are mainly the expression of an autosomal dominant gene which lacks penetrance in both sexes, but with a much lower penetrance in the female than in the male, perhaps about one-seventh as much.

Gout is a disease in which the average age of recognition is in the middle or later life and the lack of penetrance observed might be dependent upon the low age of the population studied. The relationship of age to serum uric acid level was tested by computing the coefficient of correlation ( $r$ ). The determination was made for each sex separately. The value of  $r$  with its standard error was found to be  $+0.088 \pm 0.129$  for male relatives of gouty people. This shows complete lack of correlation indicating that there is no significant increase of the serum uric acid in males after the age of 20. No alteration in penetrance is to be expected with advancing years. The finding in regard to women is quite different. Here  $r$  was found to be  $+0.44 \pm 0.09$ , a degree of correlation which is definitely significant. A marked difference is thus revealed between men and women. Inspection of the correlation table shows that every woman with hyperuricemia was over 50 years of age, a fact which suggests that normal menstrual function inhibits the development of idiopathic hyperuricemia.

Whether the level of serum uric acid is definitely established for men at adolescence or earlier in childhood is at present unknown. The present series included only eight males below the age of 20, so that our observation on this point is limited. Talbott, however, observed hyperuricemia in four males under the age of 20, the youngest being 14. His observations differed from ours also regarding the age of females. Among the relatives of gouty patients, he records seven hyperuricemic women all under the age of 42, the youngest being 21.

From the above considerations we tentatively conclude that hyperuricemia is an autosomal dominant with low penetrance in both sexes, but considerably lower in the female than in the male. Since it is desirable wherever possible to put the conclusion to the numerical test, even when the data for making such a test may be somewhat inadequate and inconclusive, we have assembled the pertinent data from table 3 in table 7. It is well known that in analyzing human genetic data a correction must be made for small family size. When families are small, certain families of the proper genetic constitution but having several unaffected offspring will go unrecognized and therefore uncounted. The observed affected offspring will consequently be more than the theoretically expected number.

Hogben<sup>6</sup> has published tables of corrective factors for families of different size. These tables are for testing ratios in fraternities for genes with

With mothers affected all sons become involved. Fathers do not transmit to their sons. This situation is approached in this series in that six of eight sons of five affected mothers had gout. Fathers, however, do not transmit sex-linked characters to their sons but only produce carriers of their daughters. In this series three fathers transmitted gout to their sons, table 3, Nos. 7, 14, 38. Smyth and Freyberg<sup>6</sup> described two similar instances. The data do not support the theory that gout or hyperuricemia are sex-linked characters.

The possibility that hyperuricemia might be a recessive trait was tested in the following way: When one parent shows a trait and some of the children are affected, the other parent may be normal if the trait is dominant. If the trait be recessive, however, the phenotypically normal parent must be heterozygous or affected children will not appear. It is obvious that there must be a sufficient reservoir of heterozygotes in the population to give a reasonable probability that the required number of matings may occur with random mating. In other words the genetic analysis of the data of the pedigrees must be consistent with the gene frequencies in the population.

Since about one-eighth of the relatives of gouty people were found to have unsuspected hyperuricemia it seemed reasonable to suppose that this trait might be observed in a discoverable proportion of the general population selected at random. In an effort to test this supposition, routine serum uric acids were done on patients on the medical wards at City Hospital, care being taken only to exclude known gout. Of 1,024 determinations on 961 patients, only 59 or 5.7 per cent were over 6.4 mg. per 100 c.c. Those included 25 tests on patients with urea nitrogen retention, 16 with cardiac failure, eight malignant growths or leukemia, two pneumonia, four anemia or recent hemorrhage, and three, all below 6.8 mg., who subsequently had lower values and were considered normal. Only one patient, a diabetic, had a level of 9.1 mg. per 100 c.c., the only one of 961 individuals tested who might be considered to have constitutional hyperuricemia. This result was sufficient to discourage further attempts to discover the true incidence of constitutional hyperuricemia in the general population by this method.

Despite the obvious inadequacy of these data they were used tentatively as a basis for gene frequency analysis. Instead of using 1 in 1,000 for the proportion of hyperuricemia in the general population this figure was arbitrarily adjusted to 3 in 1,000 in order to be conservative in the conclusions. This assumption weights the argument strongly in favor of the theory that hyperuricemia is inherited as a recessive. Despite this advantage the theory earns little support in the following argument.

With hereditary characters the frequencies of homozygous dominants, heterozygotes, and homozygous recessives in a population mating at random agree with the equation  $d^2 + 2dr + r^2 = 1$ , where  $d$  (the frequency of the dominant gene)  $+ r$  (the frequency of the recessive allele)  $= 1$ . If the incidence in the population is assumed to be 3 per 1,000, and the gene for the trait is dominant,  $d = 0.0017$ ,  $r = 0.9983$  and the corresponding frequencies

tion to high uric acid concentrates in the blood. These factors still remain unidentified despite intensive investigation for many years.

### SUMMARY

This study is based on 248 serum uric acid determinations on the 201 members of 44 gouty families as well as 1,024 serum uric acids on 961 patients examined routinely at City Hospital. A clear-cut division between hyperuricemia and normal was recognized clinically at 6.5 mg. per 100 c.c., which was confirmed by statistical analysis. The incidence of hyperuricemia in the relatives of gouty patients was found to be 18 per cent among 11 mothers, 17 per cent among 24 brothers, 21 per cent among 24 sisters and 15 per cent among 33 sons. Not a single daughter among 45 tested was found to have hyperuricemia.

There was no correlation between age and hyperuricemia among male relatives of gouty patients, but a significant correlation was found among female relatives. Since no female relative in this series was affected below the age of 50, it seems possible that normal menstrual function inhibits hyperuricemia.

On the assumption that gout and the hyperuricemia found in some of the relatives of gouty patients are the expression of the same genotype both in the same family and in different families, this series was developed in an attempt to detect the genetic mechanism involved. The genetic peculiarities of hyperuricemia are such that in some families it resembles an autosomal recessive, whereas in others it is more like an autosomal dominant. These peculiarities are, however, quite satisfactorily explained if the gene involved is an autosomal dominant which lacks penetrance in both sexes, but has a much lower penetrance in the female than in the male. A tentative estimate of the penetrance is about 84 per cent in the heterozygous male, about 12 per cent or less in the female. This conclusion brings the data of the pedigrees in good agreement with a tentative estimate of the gene frequencies in the general population.

*Note:* Since this article was submitted for publication, three studies have appeared which are pertinent to the subject: SMYTH, C. J., COTTERMAN, C. W., and FREYBERG, R. H., JR.: The genetics of gout and hyperuricemia—an analysis of 19 families, *Jr. Clin. Invest.*, 1948, xxvii, 749-759; SMYTH, C. J., STECHER, R. M., and WOLFSON, W. Q.: Genetic and endocrine determinants of the plasma urate level, *Science*, 1948, cviii, 514-515; HELLMAN, L.: Production of acute gouty arthritis by adrenocorticotropin, *Science*, 1949, cix, 280-281.

### BIBLIOGRAPHY

1. McCracken, J. P., OWEN, P. S., and PRATT, J. H.: Gout: still a forgotten disease, *Jr. Am. Med. Assoc.*, 1946, cxxxix, 367-372.
2. BROCHNER-MORTENSEN, K.: One hundred gouty patients, *Acta med. Scandinav.*, 1941, cvi, 81-107.
3. FOLIN, O., and DAVIS, W.: The diagnostic value of uric acid determinations in blood, *Arch. Int. Med.*, 1915, xvi, 33-37.

# THE USE OF CURARE (D-TUBOCURARINE IN OIL AND WAX) IN THE TREATMENT OF MUSCLE SPASM IN RHEUMATIC DISORDERS \*

By H. M. MARGOLIS, M.D., F.A.C.P., and PAUL S. CAPLAN, M.D.,  
*Pittsburgh, Pennsylvania*

THE present report records our preliminary observations in a consecutive series of 58 cases of various types of rheumatic disease in which treatment with curare in oil and wax was instituted. Curare was administered in 51 cases in which muscle spasm actually existed. The remaining seven cases were those in which a diagnosis of psychogenic rheumatism was made. In these, subjective symptoms of "muscle stiffness" without objectively demonstrable spasm were prominent along with many other bizarre musculo-skeletal symptoms. Curare was used in this group primarily for control purposes, as an aid in evaluation of results in the larger group. Although the number of patients studied is not large, the results have been definitive. The conclusions to be drawn with regard to the effectiveness of the drug in the various syndromes studied are unmistakable. This preliminary report may indicate not only the area of usefulness of the drug, as revealed by our experience, but may encourage further interest in its study in other, related types of rheumatic disease.

The historical background of the use of curare, the pharmacologic properties of which were first demonstrated by Claude Bernard as far back as 1850, and its physiologic properties, as well as its more recent applications have been well described in a series of publications by Schlesinger and Ragan.<sup>1, 2, 3, 4, 5</sup>

Briefly, tubocurarine is a quaternary ammonium salt. These salts, as a group, possess the property of paralyzing conduction at the myoneural junction. In certain concentrations, tubocurarine has an almost pure myoneural junction effect. This neuromuscular block can be employed therapeutically, because with certain specific concentrations of curare as employed in the present study, involuntary muscle spasm is abolished, whereas voluntary muscular contraction is entirely unaffected.

The effect of curare in creating myoneural block has been known for many years. Practical application of this knowledge was not possible, however, until recently, when a crystalline derivative of the crude alkaloid, with predictable pharmacologic properties and toxicity became available. The earlier aqueous preparations of curare were not well suited to the treatment

\* Received for publication May 18, 1948.

From the Department of Medicine and the Arthritis Services of The Montefiore and St. Margaret Memorial Hospitals and The John C. Oliver Memorial Research Foundation of The St. Margaret Memorial Hospital.

The results were recorded as either definitely beneficial; not beneficial; questionably beneficial.

Results were tabulated as definitely beneficial only when striking relief of symptoms occurred with curarization (estimated at an average of 85 per cent). These findings were confirmed by objective examination.

Results were tabulated as questionable when the patient reported slight subjective improvement which could not be confirmed by objective examination. In many instances it was felt that subjective change could not be directly attributed to curarization.

### ANALYSIS OF RESULTS

*Rheumatoid Arthritis.* There were 23 cases of generalized rheumatoid arthritis. The duration of the disease varied from one to 20 years, the majority of the patients (16 cases) having been ill for over five years. All presented typical clinical and roentgenographic evidence of rheumatoid arthritis; all were in a stage of activity as indicated clinically and by rapid sedimentation rates, and many of them showed characteristic deformities. These patients received three to six injections of 175 units (1.0 c.c.) of curare in wax and peanut oil every two to three days; this treatment was continued with one patient for a period of six weeks. In several instances reactions without relief of muscle spasm were noted following injection. In these cases administration of the drug was discontinued.

In none of these patients was there clinical evidence of definite improvement, either subjective or objective. In five cases there was questionable subjective improvement which could not be confirmed by examination. It is perhaps significant that of these five, one was suffering from Marie-Strumpell (rheumatoid) spondylitis and four presented evidence of Marie-Strumpell spondylitis associated with rheumatoid arthritis of peripheral joints. Three cases of typical rheumatoid spondylitis, however, were not benefited either subjectively or objectively.

*Periarthritis of Shoulder.* There were five cases of periarthritis of the shoulder. The roentgenograms in all were normal.

These patients presented the characteristic symptoms of pain in the shoulder and along the course of the deltoid muscle, pain always increased by attempts at abduction, external or internal rotation of the arm. In all cases normal range of motion was to some degree restricted. Definite adhesive changes limiting the range of mobility were associated in two. In these, manipulation of the shoulder under anesthesia was performed. In the other three cases restriction in the range of motion was caused entirely by muscle spasm. In one of these, manipulation of the shoulder was performed in the course of tonsillectomy, but no adhesions were present.

In all five cases of periarthritis of the shoulder there was distinct improvement, both subjectively and objectively, attributable to the administration of curare. In the two cases in which manipulation was performed to break



*Osteoarthritis with Associated Periarticular (Capsular) Fibrositis.* Six patients with clinical and roentgenographic evidence of osteoarthritis of peripheral joints with associated periarticular (capsular) fibrositis of either degenerative or perhaps infectious origin were treated.

In two of these patients questionable subjective improvement resulted from the administration of curare. Both were elderly. In both the onset of the fibrositic symptoms followed an acute respiratory infection; the sedimentation rates were accelerated. The findings indicated a capsulitis of apparently infectious origin, superimposed upon marked generalized osteoarthritis. Although these patients reported some alleviation of morning stiffness, the effect was negligible and probably attributable to the general therapeutic measures; rest, analgesics, and physiotherapy used concomitantly with curare.

Four of these patients presented osteoarthritis of the peripheral joints with symptoms indicative of an associated capsulitis of degenerative origin. They all had normal sedimentation rates. In none of these was there evidence of improvement, either objective or subjective, after repeated administration of curare in oil and wax.

*Fibromyositis.* Four patients with fibromyositis failed to derive any benefit from repeated administration of curare. One of these patients suffered from a generalized fibromyositis following an acute upper respiratory infection. The second patient manifested characteristic fibromyositic symptoms involving the shoulders, hips, and lower back. The fibromyositis in the third and fourth patients was localized to the cervical region.

*Psychogenic Rheumatism.* Seven patients presented the typical syndrome of psychogenic rheumatism in which a feeling of stiffness, muscle aching, and other types of pain, often bizarre, were associated with other psychoneurotic personality traits. A diagnosis of psychogenic rheumatism had previously been established both by direct examination as well as by exclusion of organic musculoskeletal disease. There was no hope of obtaining any therapeutic benefit in this group; they served as a control. In none of these cases was any improvement noted. Two patients described some degree of subjective improvement, but this, however, did not correspond to the usual description of the effect of curare. Subsequent injections of curare were said to have been of no benefit or to have been followed by actual increased severity of symptoms.

## DISCUSSION OF RESULTS

The beneficial effects of curare are always evidenced by prompt, dramatic relief of muscle spasm, generally after the first injection of the drug. Hence, long periods of trial are unnecessary. The specific physiologic effect of the drug is so clear cut that when beneficial therapeutic results are forthcoming, they should be evident to some degree after the very first injection. Except in the case of patients with psychogenic rheumatism, the response is generally

ployed in conjunction with physiotherapy and manipulative exercises. By overcoming muscle spasm, it may be possible in some of these instances to restore the full range of motion in the shoulder by physiotherapeutic measures, including exercise, when manipulative therapy under anesthesia might otherwise be required. The use of curare is also strikingly beneficial in conjunction with physiotherapeutic measures which we institute promptly after the breaking up of adhesions under anesthesia. In such cases we have found that the therapeutic exercises following manipulation were carried out more easily, with less discomfort, and with a better ultimate result, attained in a much shorter period of time. The number of cases so treated is small, however, so that final evaluation is not possible at this time.

The beneficial results of curare in the relief of low back pain demonstrates the specific value of this drug in the abolition of reflex muscle spasm. Curare should find its greatest field of usefulness in the treatment of low back pain when there is muscle spasm of reflex origin. Our two patients with low back pain (without sciatic radiation) who were not benefited from curare presented associated factors, especially an unfavorable psychogenic component which militated against a favorable result. Their evidence should therefore not detract from the otherwise consistently favorable results in this group of cases.

We found curare to be of no value in low back pain with sciatic radiation caused by nerve root irritation or pressure. These results confirm the observations of Schlesinger and Ragan<sup>4</sup> who also noted that with removal of the splinting action of muscle spasm, sciatic pain resulting from direct nerve root involvement was increased.

Relief of muscle spasm and pain which the use of curare affords in the treatment of periarthritides of the shoulder and low back pain is dramatic. It would be unsound, of course, to discard other proved therapeutic measures specifically applicable to the underlying pathologic lesion. The contribution of curare is the abolishment of the cycle of muscle spasm and pain which often constitutes a most trying and protracted problem. Earlier rehabilitation of the patient is then possible.

In the treatment of osteoarthritis of peripheral joints with associated degenerative periarticular (capsular) fibrositis, curare is generally unsatisfactory. Since the restriction of mobility and pain in these cases is related largely to changes in the joint cartilage and articular capsule and not primarily to reflex muscle spasm, the absence of a favorable response to therapy with curare is not surprising.

Curare has also proved totally ineffective in the syndrome of fibromyositis.

The lack of benefit to be derived from the use of curare in cases of psychogenic rheumatism merely serves to define more sharply the specific problems in which it may be helpful.

Reactions followed the administration of curare in 12 of the 58 patients. For the most part reactions were mild and not disabling, and consisted of

ness. Prostigmine, an antagonist to curare, may be employed to overcome the more severe reactions.

#### BIBLIOGRAPHY

1. SCHLESINGER, E. B.: The use of suspension of tubocurarine in oil in the treatment of spasticity, *Arch. Neurol. and Psychiat.*, 1946, 1v, 530.
2. SCHLESINGER, E. B.: Recent advances in the use of curare in clinical practice, *Bull. N. Y. Acad. Med.*, 1946, xxii, 520.
3. SCHLESINGER, E. B.: Curare: a review of the therapeutic effects and their physiological basis, *Am. Jr. Med.*, 1946, 1, 518.
4. SCHLESINGER, E. B., and RAGAN, C.: "Muscle spasm" in acute low back pain and similar syndromes, *Am. Jr. Med.*, 1946, 1, 621.
5. SCHLESINGER, E. B.: Therapeutic applications of curare and their physiologic implications, *N. Y. State Jr. Med.*, 1947, xlvii, 1689.
6. STEINER, G., FREUND, H. A., LICHENTRITT, B., and MAUN, M. E.: Lesions of skeletal muscles in rheumatoid arthritis. Nodular polymyositis, *Am. Jr. Path.*, 1946, xxii, 103.

well, requiring only 20 to 30 units of insulin per day) some 20 others have been reported.

In these radical procedures, the operative risk, the long term followup, and the comfortable physiology and relief from pain and jaundice depend upon several factors: (1) the type of the carcinoma, (2) the site of the tumor, (3) the early diagnosis of the lesion, before it has spread to the lymph nodes and peritoneum, (4) the radical, en bloc, removal of the growth with part or all of the pancreas, the entire duodenum, the lower end of the common duct, the antrum of the stomach, and the retroduodenal and pancreatic lymph nodes.

### THE TYPE OF CARCINOMA

Carcinoma of the papilla of Vater and the ampullary area is usually a fungating adenocarcinoma, growing into the lumen of the duodenum with a slower invasion of the lymphatics. Carcinomas of the pancreas are more often of the invasive, infiltrating, undifferentiated type, spreading rapidly into the lymph nodes and metastasizing to the liver and peritoneum.

### THE SITE OF THE TUMOR

Ampullary growths obstruct the bile and pancreatic ducts more quickly and completely than those in the pancreas, and give the important warning signal of jaundice earlier. Courvoisier's syndrome of painless jaundice with an enlarged gall bladder is most frequently seen in the patients with ampullary tumors. However, not all of these patients are pain-free, yet the pain is not as severe, constant, or radiating to the back as it is in pancreatic carcinomas of the body or tail.

In carcinoma of the pancreas, the warning signal of jaundice depends upon the proximity of the growth to the common duct. It is usually absent in carcinoma of the body and tail. Pain, as mentioned, is usually more severe and constant, worse on lying down and frequently of a boring character, radiating into the back. The more distant from the ampulla, the later the diagnosis as a rule, and the worse the prognosis.

### EARLY DIAGNOSIS

Aside from the essential history and physical examination, which in many patients establishes the early diagnosis, certain laboratory procedures are helpful and must be emphasized. The most important is the study of the duodenal contents. This is based upon the early sound observations of Pavlov,<sup>6</sup> who demonstrated the effect of increased pancreatic external secretion by vagal stimulation, and of Bayliss and Starling,<sup>7</sup> who demonstrated the hormonal action of secretin in accelerating the flow of pancreatic juice. Since then, Lagerlöf<sup>8</sup> in Stockholm, Comfort<sup>9</sup> and his associates at the Mayo Clinic, and Bauman<sup>10</sup> at the Columbia-Presbyterian Clinic in this country have demonstrated the value of duodenal intubation in the differen-

patients lived five years or more, after removal of ampullary growths—two of them over seven years. Of the collected cases of carcinoma of the pancreas, three have survived five years or more,—two of them operated upon by Brunschwig.<sup>14</sup> One of these, the first one stage radical resection for carcinoma of islet cells, is living over nine years, but may have liver metastases at present. This is not a functioning islet cell tumor, however. In Cattell's<sup>11</sup> largest series of 59 patients operated upon for carcinoma, 30 per cent lived three years or more.

The fact that it has been demonstrated that cancer cells can be readily found in pancreatic duct fluid in cases of pancreatic carcinoma, and that trypsin favors the transplantation of cancer cells in experimental animals<sup>15</sup> would explain the high incidence of recurrence in resection of the pancreas, and may be a definite indication for a total pancreatectomy in patients with carcinoma of the pancreas.

#### BIBLIOGRAPHY

1. KAUSCH, W.: Das Carcinom der Papilla duodeni und seine radikale Entfernung, Beitr. klin. Chir., 1912, lxxviii, 439-486.
- HIRSCHEL, G.: Die Resektion der Duodenums mit der Papille wegen Karzinoms, Munchen. med. Wchnschr., 1914, lxi, 1728.
- TENANI, O.: Contributo alla chirurgia della papilla del Vater, Policlinico, 1922, xxix, 291.
2. HOWLAND, G., CAMPBELL, W. R., MALTBY, E. J., and ROBINSON, W. L.: Dysinsulinism; convulsions and coma due to islet cell tumor of pancreas, with operation and cure, Jr. Am. Med. Assoc., 1929, xciii, 674-679.
3. WHIPPLE, A. O., PARSONS, W. B., and MULLINS, C. R.: Treatment of carcinoma of the ampulla of Vater, Ann. Surg., 1935, cii, 763.
4. WHIPPLE, A. O.: Pancreatoduodenectomy for islet cell carcinoma: a five year followup, Ann. Surg., 1945, cxxi, 847.
5. PRIESTLEY, J. T., COMFORT, M. W., and RADCLIFFE, J.: Total pancreatectomy for hyperinsulinism, Ann. Surg., 1944, cxix, 211.
6. PAVLOV, J. P.: Die Arbeit der Verdauungsdrüsen, 1898, Wiesbaden.
7. BAYLISS, W. M., and STARLING, E. H.: The mechanism of pancreatic secretion, Jr. Physiol., 1902, xxviii, 325.
8. LAGERLOF, H. O.: Pancreatic function and pancreatic disease studied by means of secretin, 1942, P. A. Norstedt and Soner, Stockholm.
9. COMFORT, M. W., PARKER, R. L., and OSTERBURG, A. E.: Concentration of pancreatic enzymes in the duodenum of normal persons and persons with disease of the upper abdomen, Am. Jr. Digest. Dis., 1939, vi, 249.
10. BAUMAN, L., and WHIPPLE, A. O.: The diagnostic value of pancreatic function tests in 47 surgically treated patients, Am. Jr. Med. Sci., 1944, ccvii, 281.
11. CATTELL, R. B., and PYRTEK, L. J.: An appraisal of pancreatoduodenectomy: a followup study of 61 cases. Read before the Southern Surgical Association Meeting, Dec. 6, 1948; to be published in Ann. Surg., 1949. Also personal communication, March 8, 1949.
12. LOCKWOOD, J. S.: Personal communication, March 28, 1949.
13. WAUGH, J. M.: Personal communication, March 15, 1949.
14. BRUNSCHWIG, A.: Personal communication, March 20, 1949.
15. HOWES, E. L.: Experiments not yet published. Quoted by Dr. Lockwood.

period of observation of these patients was often shorter than desirable, so that in many instances the daily dose of insulin was considerably more at the time of dismissal than it subsequently became at home, and the control of glycosuria in some instances was not the best attainable.

The fact that the response of diabetic patients to treatment differs is frequently overlooked. That such variability actually exists is illustrated by the well-known fact that in almost half of all cases of diabetes the disease is well controlled by diet therapy alone, while in the other half insulin in addition to diet is necessary. Furthermore, among patients who require insulin there is a great variability in response to treatment. The reasons for this variability are not well understood. It may perhaps indicate that there are different forms of the disease, different etiologic factors, or possibly only differences in the intensity of the disease. In any event, it is important to be aware of the inherent ease or difficulty of therapy in different diabetic patients before a program of administration of insulin is chosen in any given case, and before the merits of any particular system of therapy employed in a group of cases are judged.

Stated simply, in some diabetic patients the disease is easily controlled by almost any program of administration of insulin, whereas in others the timing characteristic of the action of the insulin employed must be carefully tailored to the needs of the individual. In the latter group of cases a relatively intense insulin action usually is needed during the day when food is being ingested, and a relatively feeble insulin action, during the fasting hours of the night. Insulin therapy to be effective in cases of severe diabetes must be arranged so that account is taken of the fact that the human subject eats during the day and fasts during the night. Furthermore, there is a small group of patients—those who have so-called unstable or brittle diabetes—in whom it is virtually impossible to maintain sugar-free urine and freedom from insulin reactions with any type or combination of insulins now available. In this group it seems that nothing short of an “automatic” insulin, with rate of absorption determined by the level of the blood sugar, would accomplish precise control. Unfortunately, there is at present no indication that an insulin with such a high order of intellect will ever be developed.

#### DEVELOPMENT OF THE USE OF MIXTURES OF INSULIN

In this country Colwell,<sup>2</sup> MacBryde,<sup>3</sup> Peck<sup>4</sup> and others have made intensive studies of the action of mixtures of regular and protamine zinc insulin in diabetic patients. Colwell,<sup>2</sup> in particular, in a series of excellent papers published since 1942, has described with considerable precision the timing characteristics of mixtures of varying proportions of regular and protamine zinc insulin. Briefly, it has been shown that it is necessary to mix at least one part of regular with one part of protamine zinc insulin to secure definite modification of the action of the latter. Intensification and shortening of action is not sufficiently marked to be therapeutically useful

well's descriptions of their action, arrived at by rigidly conducted experimentation.

One further digression is necessary before proceeding to a consideration of the treatment employed in our recent group of cases. This concerns the vexing questions of what constitutes control of diabetes and, once control has been defined, how important is it? Is it necessary to set one's therapeutic goal any higher than the simple avoidance of ketosis and severe insulin reactions? These questions have not yet been answered satisfactorily, and he who pretends to know the answer is basing his opinion more on feeling than on actual knowledge. I am personally of the opinion that control (or lack of it) is probably not the only, or even the crucial factor in the prevention (or development) of the so-called degenerative complications of diabetes, arteriosclerosis, retinopathy, neuropathy and intercapillary glomerulosclerosis, which are being observed with increasing frequency among diabetic patients who have been kept alive for many years by use of insulin. Nevertheless, as Ricketts<sup>6</sup> has pointed out, the burden of proof is on the one who says that control is unimportant. Prolonged periods of unbridled glycosuria, perhaps associated at times with mild ketosis, might well be one factor in the development of degenerative complications, even if not the sole factor. Therefore, until the contrary is proved, we should continue to strive for as precise control of glycosuria as is possible and compatible with a reasonably simple program of treatment and the avoidance of insulin reactions.

#### TYPES OF INSULIN THERAPY RECENTLY EMPLOYED

Now to proceed to a consideration of the types of therapy employed in the recent group of 246 ambulatory diabetic patients. This particular number of patients was chosen for study because it included exactly 100 patients who were treated with extemporaneous mixtures of regular and protamine zinc insulin. These 100 patients will be subjected to closer scrutiny than the rest because it is treatment with such mixtures that interests us at this time.

First, it will be noted that of the total of 246 patients, 96 (or 39 per cent) required only diet therapy, without the use of insulin, for control of glycosuria (table 1). We have made a practice of omitting insulin only in those cases in which the urine is demonstrated to remain consistently free of sugar while the patient is on an adequate diet without the use of insulin. This figure is somewhat lower than that for the total diabetic practice of the clinic,

TABLE I  
Therapy Employed Recently in 246 Cases  
of Diabetes Mellitus (1948-1949)

Therapy	Cases	Per cent
No insulin	96	39
Insulin	150	61

experience, these same patients get along equally well with mixtures, and we believe more safely. Indeed, it seems that all patients now treated with protamine zinc insulin would fare equally well with an insulin having timing characteristics intermediate between those of protamine zinc and regular insulin.

It has already been pointed out that in the early days of the use of mixtures it was found by a rather tedious process of clinical trial and error that the best control of severe diabetes and the greatest freedom from insulin reactions were attained with mixtures containing 2 or 3 units of regular insulin for every 1 unit of protamine zinc insulin. The experience of recent years has continued to verify this early impression. The strong effect of such mixtures tends to prevent excessive glycosuria during the day, while the prolonged effect prevents escape from control overnight. There is sufficient

TABLE IV  
Mixtures of Regular and Protamine Zinc Insulin  
in 100 Cases of Diabetes Mellitus

Ratio of regular to protamine zinc insulin	Cases
Less than 1:1	2
1:1 to 1.5-:1	4
1.5:1 to 2-:1	19
2:1 to 2.5-:1	54
2.5:1 to 3-:1	13
3:1 and higher	11

overlapping of the effects of doses on successive days to provide additional insurance against serious loss of control due to the waning of action of one dose before the next one begins to act. The more severe the diabetes, or the higher the carbohydrate content of the diet, the more likely is the ratio to be in the neighborhood of 3:1 rather than 2:1. It will be noted that for 67 of the recent series of 100 patients treated with mixtures, the ratio of regular to protamine zinc insulin was between 2:1 and 3:1 (table 4). With longer periods of observation of the patients the proportion of mixtures in this range would probably be increased, for many of the patients who had mild diabetes and used low ratios at the time of dismissal eventually were stabilized on small doses of protamine zinc insulin alone.

#### DIFFICULTIES IN THE USE OF MIXTURES

It is perhaps unnecessary to point out that mixtures do not solve all the problems of treatment of patients who have diabetes of the type which has been described as "brittle," "labile" or "unstable." The diabetes of a few of these patients remains difficult to control with mixtures or any other form of insulin therapy. While these patients have the most severe type of diabetes from the standpoint of difficulty of control, they do not necessarily



more, it can be expected to give satisfactory results in all the patients who are now successfully treated with small doses of protamine zinc insulin alone. In the few cases of severe diabetes in which higher ratios of regular to protamine zinc insulin are required, supplementation with additional amounts of regular insulin is easily accomplished in accordance with the needs of the individual patient. Fortunately, the addition of small amounts of regular insulin to insulin type NPH 50, unlike the addition to protamine zinc insulin, results in definite intensification of its action.

The principles involved in the adjustment of the two kinds of insulin comprising a mixture are relatively simple. In the first place, as has already been mentioned, it was learned by experience some time ago that the majority of patients who are treated with mixtures of insulin obtain the best control when the amount of regular insulin is two to three times the amount of protamine zinc insulin. In the actual regulation of diabetes of a patient, one can proceed as follows: The test for sugar in a fresh specimen of urine voided in the morning before breakfast is used as a criterion of the adequacy of the dose of protamine zinc insulin taken 24 hours previously. The dose is so adjusted that there will be no nocturnal reactions, and little or no sugar in this specimen, preferably none. Likewise, the test of a fresh specimen voided late in the afternoon before supper serves as an index of the adequacy of the dose of regular insulin taken that morning. This dose is adjusted so that reactions will not occur during the day, and there will be no more than a trace of sugar in this specimen. Changes in the dose of protamine zinc insulin are usually made in steps of 2 units, since this dose is relatively small, while changes in the dose of regular insulin, which is usually at least twice as large, are usually made in steps of 4 units. The patients are carefully instructed in the method of adjustment, for frequently further adjustments of the dose are necessary at home, particularly if the period of observation under the direct supervision of the physician is short.

### SUMMARY

The timing characteristics of appropriate mixtures of protamine zinc and regular insulin are well adapted to the needs in many cases of moderately severe to severe diabetes. Such mixtures provide the requisite intensity of insulin action during the day when food is being ingested, and a prolonged action of low intensity for maintenance of control of diabetes overnight. An effective proportion in most instances is between 2 and 3 units of regular insulin to 1 unit of protamine zinc insulin.

A fixed modification of protamine zinc insulin having an action like that of a 2:1 mixture of regular and protamine zinc insulin such as insulin type NHP 50, could be employed with satisfactory results in many more cases than the standard protamine zinc insulin which is now available. Its action could be further intensified and shortened by the addition of regular insulin when necessary.

# SUMMARY OF EVIDENCE RELATING LIFE SITUATION AND EMOTIONAL RESPONSE TO PEPTIC ULCER \*

By STEWART WOLF, M.D., *New York, N. Y.*

THE evidence connecting the occurrence and recurrence of peptic ulcer to emotional conflicts in the life situation has been recently reviewed by Wener and Hoff.<sup>1</sup> The relationship has not as yet been definitely established, but on the basis of studies from several points of view and with a variety of technics, it seems highly likely that some peptic ulcers, at least, occur as part of a biologic pattern which is set in motion in reaction to stresses and strains involving chiefly problems of interpersonal relationship. The data in support of this view are outlined briefly below.

First, it has been known for many years that the stomach of the subject with duodenal ulcer is a hyperfunctioning one, that is, it is red, secretes relatively large amounts of acid, is relatively hypermotile and empties in a comparatively short time. When it has been possible to induce experimental peptic ulcer in animals, the condition has been preceded and accompanied by intense engorgement of the gastric mucosa.<sup>2, 3, 4</sup>

In our studies on the fistulous subject, Tom, we found by direct observation of the gastric mucosa and simultaneous collections of gastric juice and recording of motility that this hyperfunctioning state could be induced by situations which engendered anxiety associated with feelings of hostility and resentment.<sup>5</sup> We found, moreover, that the stomach under these circumstances was hyperemic, turgid and engorged. When, under circumstances of sustained resentment, this pattern of gastric hyperfunction was prolonged, the pain threshold of the stomach was significantly reduced. This led to localized epigastric pain following the application of stimuli such as pinching or Faradic current, which were ordinarily non-noxious. Likewise, gastric contractions of a force and magnitude which would ordinarily not arouse sensations became painful. Thus, in the absence of ulceration but in the presence of sustained gastric hyperemia and hyperfunction, the characteristic ulcer symptoms of epigastric pain relieved by food or alkalis were frequently observed.

Not only was lowering of the pain threshold observed to accompany gastric hyperfunction in association with sustained conflict, but a second physiologic hazard was also observed under these circumstances, namely, increased fragility of the mucous membrane. When the stomach was in an

\* Presented at a Panel Discussion, Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 29, 1949.

From the Department of Medicine of Cornell University Medical College and the New York Hospital, New York, N. Y.

Aided by grants from the Commonwealth Fund and the Estate of Lester N. Hofheimer.

gical procedures considered to have divided all of the parasympathetic innervation to the stomach. Additional confirmation derives from an experiment performed in our laboratory on a second fistulous subject whose fistula was made prior to the attempted surgical removal of a carcinoma of the esophagus.<sup>7</sup> During the latter procedure, it was necessary to section the vagus nerves above the diaphragm. Thus, direct observations were available on the stomach before and after vagotomy. Experimental procedures similar to those performed on Tom were carried out on this subject, his gastric mucosa being viewed through a Brown-Buerger cystoscope. During one of the experimental periods prior to vagotomy the appearance and manner of the subject indicated a sharp change from his usual, quiet friendliness. His face was red, and he appeared exasperated and irritable. He had complained of stiffness and back pain ever since the previous experiment, and confessed that he was angry at having come down to the laboratory again in view of the apparent delay occasioned in his operation.

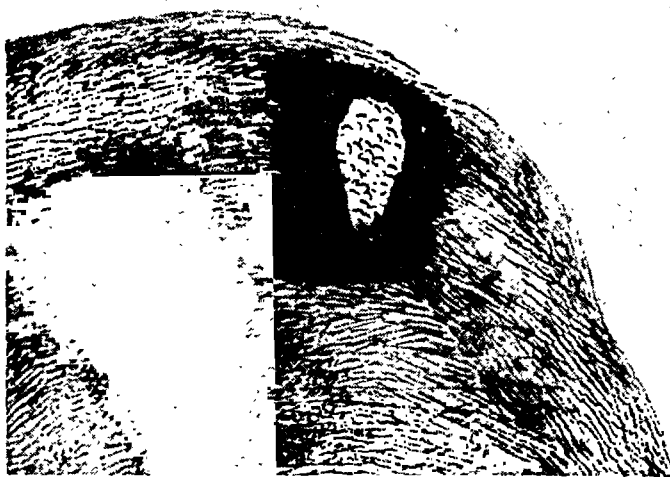


FIG. 1. Drawing of ulcerated lesion induced experimentally on the gastric mucosa of Tom.

The subject's stomach was examined and found to be much redder and more engorged than before, about 70 on the scale in contrast to the previous 50. He was more voluble and talkative. Asked about his concern regarding his condition, he said that he was reminded of the first doctor whom he had consulted for difficulty in swallowing. The latter had focused his attentions on the stomach, much to the annoyance of the patient. "He was so dumb. I told him it wasn't my stomach, because I knew I couldn't swallow right. He made me waste four weeks fooling around." On this occasion, there occurred much more spontaneous motor activity in the stomach than before. The mucous membrane was so turgid that the minor traumata incident to the instrumentation with the cystoscope caused bleeding. The subject's dominant mood during this interview was anger coupled with hostility and strong feelings of frustration. His stomach displayed the pic-

transitory and even sustained alterations in gastric function occur in company with emotional conflicts and that such changes may be associated with epigastric pain, it remains to correlate such reactions to stress with gastric changes and symptoms in subjects with the actual clinical peptic ulcer. The coincidence of onset and exacerbation of the ulcer syndrome in association with difficult life situations is a familiar bedside observation. Mirsky and associates have shown an increase in concentration of a proteolytic enzyme in the blood and urine of subjects with peptic ulcer and especially in situations of significant personal conflict.<sup>9</sup> Experimental correlation of conflict with gastric hyperfunction and symptoms was reported by Mittelman and Wolff<sup>10</sup> and more recently additional evidence on this point has been collected as detailed below.

*Case 1.* A 44 year old civil service employee had complained of gnawing epigastric pain on and off for 20 years. His father had been a gentle, retiring person and his mother a matriarchal woman, intensely ambitious for her children. His two older brothers were able to adjust satisfactorily to this setting, the oldest by graduating from medical school, the second one by adopting a rebellious attitude and becoming a professional gambler instead of a lawyer as his mother had wished. The patient felt the need to compensate for his brother's indifference, and took pre-medical work in college. He did poorly, and tried engineering instead. After failing that, he abandoned college. In this setting, he had his first symptoms of epigastric pain, and a duodenal ulcer was demonstrated by radiologic examination. He later obtained a civil service job as a draftsman, and became engaged to a warm, sympathetic girl. Symptoms disappeared during this interval, until the girl died of rheumatic heart disease a few months later. The patient's mother also died at approximately the same time. Within a few months he married an authoritarian, cold and financially ambitious woman. She disapproved of his social relationship with men friends, and eventually forced him to give up lodge activities, from which he derived great satisfaction. Shortly after his marriage, the patient's ulcer symptoms recurred, and they have remained chronic ever since. Several exacerbations and two episodes of hemorrhage have coincided with periods in which his wife seriously disparaged his competence as a man. The following experiment, shown graphically in figure 3, illustrates the relevance of his conflicts concerning his wife to his gastric disturbance.

Ten minutes after the end of a spontaneous period of vigorous gastric motor activity and during a period of almost complete absence of contractions, an interview was undertaken in which the patient was reminded that, in contrast to the high regard in which he had been held by his lodge associates, his wife considered him inadequate as a provider, companion and sexual partner. He became grim and tense, clenched his jaws frequently and said, "it's been a fight all along, and now I got no more fight left in me. I'm caught like a rat in a trap." Promptly, forceful gastric contractions began, and by the end of the interview, a state of incomplete tetanus had been established. Acid secretion was also greatly enhanced, exceeding the level observed during the earlier period of spontaneously increased gastric function. By this time, the subject had begun to groan with pain. Shortly thereafter, during attempts at reassurance and diversion, the evidences of gastric hyperfunction subsided, and with them the symptoms.

*Case 2.* A 34 year old Italian income tax collector had his first episode of ulcer pain at age 16 in a setting of conflict with his father over retaining a job as auto paint sprayer, which he considered beneath his capabilities. The patient had resented his father from an early age. "My earliest recollection is lying awake at night worrying and thinking about the way my father was making sexual advances toward

my mother. I was always relieved if I saw my father go to bed first and my mother stay in the kitchen." The father was a cold, irascible individual who shared the "old country" point of view that a man's sons should work to support him as soon as they could be taken from school. The patient, on the other hand, was eager to go through college and become an engineer. He had grown up in a neighborhood in which there were a good many Jews, and it was a common pattern among the Jewish parents to make unusual sacrifices to provide professional education for their children. Both the patient's father and his younger brother, who also was caught in a conflict between the cultural pattern of his father and his neighborhood, developed peptic ulcers. In addition to his limited educational opportunities, the patient felt that another serious handicap was his small stature. He effected a truculent manner as a child, and got into a great many fights, which he considered "prophylactic," as a means of avoiding being "pushed around" by other people. He could not bear to be laughed at, and was especially sensitive to any slight, real or imagined, to his dignity and competence. He finally obtained a job as an income tax collector, and married an ambitious woman. They had one daughter. He always had difficulty satisfying his wife sexually because of premature ejaculation. She was also dissatisfied with his fixed earnings and lack of progress in the civil service job. The patient noted epigastric pain off and on with exacerbations during periods of stress and conflict and remissions during periods of relative security. "It makes me worse if anyone crosses me. I tighten up and my stomach hurts. When I can relax my stomach improves." He had a gastrointestinal hemorrhage which occasioned admission to the hospital, when a conflict developed between his wife and his favorite sister. During his period of hospitalization he improved markedly with rest, reassurance and without special attention to diet except for frequent feedings. During an asymptomatic period he was intubated with a recording balloon and a Levine tube for collection of the gastric juice. Specimens were withdrawn every 15 minutes. Free and total acid were determined by the usual colorimetric technics. Hydrochloric acid production was calculated with recourse to the methods of Hollander described elsewhere.<sup>5</sup> The acid values and motility pattern are recorded in figure 4. Fifteen minutes after a period of spontaneous motor activity at a time when the gastric musculature is relatively refractory, a discussion was begun of a humiliating experience which he had had on the ward. "An Italian fellow called me a name in Italian. I'm not a dope that I have to take that. He did it again. Later in the day I was lying in bed with a pain and he said 'This is a hell of a time for you to be lying in bed.' I told him it was none of his business, and not to bother me. Now he won't speak to me, and that's what I want. I think I'm entitled to the same respect I give out. Whenever anyone makes a crack at me I have two of them to throw back. I think I'm pretty sharp about solving problems." During the discussion, he was tense, restless and red-faced. Vigorous motor activity occurred and increase in acid output associated with epigastric pain. After approximately 25 minutes, the patient was strongly reassured and the conversation was turned to diverting topics. The gastric motor activity stopped and the pain subsided.

*Case 3.* A 47 year old Jewish lawyer had had peptic ulcer for 23 years. He was the only child of Russian immigrant parents. The father was a quiet, reflective, religious man, but the mother was intensely ambitious and hard-working. She and the father made severe financial sacrifices to provide the patient with an education. He did well in college and law school, and during the course of these years he changed his name to a more easily pronounced, anglicized form. He also married a Roman Catholic girl. His parents disapproved of this marriage, but condoned it, their principal concern being their son's "success in his career." Shortly after graduation from law school, he was taken into a firm of all gentile lawyers. He soon became heavily relied upon, and was doing much of the difficult work of the office. The partners persistently failed, however, to admit him to the firm. This was the source of great disappointment

and frustration, not only to himself but to his mother and wife, who, like his mother, was intensely ambitious. It was in this setting that ulcer symptoms first developed.

Finally, when it appeared that the partners could no longer exclude him from the firm, they hired a second Jewish lawyer. The head of the firm then told the patient that he felt unjustified to take one of these men and not the other into the firm. This occasion was followed by a severe episode of gastrointestinal bleeding, for which the patient was hospitalized. Finally, at the outbreak of World War II, the younger Jewish lawyer was taken into the Army. The older members of the firm were often preoccupied with matters outside the office, and thus the patient's duties and responsibilities were redoubled. He was virtually running the law office. Despite the heavy work and long hours, his ulcer symptoms disappeared, and throughout the period of the war he felt well. At the conclusion of the war, however, his associate returned from service unharmed, and again the frustrating situation was resumed. The patient's epigastric pain recurred and became incapacitating, and again he was admitted to the hospital. After a few days of rest, encouragement and strong reassurance, and while taking alkalis and frequent feedings, his symptoms again subsided.

At this point, he was intubated with a balloon attached to a kymograph. Gastric motor activity of an average type was recorded until suddenly an interview was engaged in in which the patient was asked why he had failed to meet his mother's ambitions and whether or not he felt that her sacrifices in his behalf had been justified. Almost immediately, gastric contractile activity became enhanced. He showed no evidence of tension or "nervousness" at first. He gave a restrained, well-organized and forceful justification of his life. As the account proceeded, however, his voice became stronger, and he became restless and tense, and the gastric contractions were associated with localized epigastric pain. The interview was allowed to continue for one hour and 30 minutes, when he was given 0.3 gm. of sodium amytal intravenously. At this point, gastric contractions stopped abruptly. His pain was promptly relieved, and his entire manner was altered. He clung weeping and sobbing to the examiner's hand, saying "I've tried so hard, so hard." He said that he finally felt relaxed, and was weeping with relief. After 27 minutes of freedom from pain, and while still under the influence of sodium amytal, a second interview was begun in which it was suggested that his change of name, his marriage to a Roman Catholic and his association with a gentile firm might represent an attempt to escape from identification with Judaism. Again his manner became restrained, his flow of conversation even and forceful. Gastric contractions were resumed, and although they were of much smaller magnitude, they were nevertheless painful.

*Comment.* These experiments on subjects with peptic ulcer in which painful gastric hyperfunction was induced or interrupted by appropriate manipulation of the situation established fairly clearly a relationship between the gastric disturbance and the attitudes and emotions of the subjects. They indicate that these individuals react habitually to stress with an acceleration of gastric function. They do not prove that peptic ulcer is caused by such sustained gastric hyperfunction, but they support this view. Further data were adduced from study of a fistulous human subject who happened also to have a peptic ulcer.

*Case 4.* A 67 year old Merchant Marine tug boat chief engineer developed obstructive symptoms with persistent vomiting and emaciation three weeks prior to his admission to the hospital. He had noted weakness and vague epigastric discomfort but he had had no history of pain suggestive of peptic ulcer except for a brief episode 30 years before which lasted only a few weeks. Roentgen-ray examination, however,

curred over a period of three weeks. Because of the esophageal stricture a gastrotomy was done. The stoma measured approximately 5 cm. in diameter and through it herniated parts of a few engorged gastric rugae. It was accordingly possible to study this subject in the same manner in which experimental observations were made on Tom and published in detail elsewhere.<sup>5</sup>

The experiment was carried out 13 hours after the last feeding and with the subject reclining comfortably on a couch. The gastric mucosa was continuously observed under standard lighting conditions. Gastric juice was siphoned through a Levine tube and motor activity was recorded on a kymograph from an inlying inflated balloon. During approximately 45 minutes of control period the subject was lightly diverted and continuously reassured. As already noted the membrane during this period was already moderately engorged (3+) and hyperemic (60 on the color scale). Gastric juice was elaborated at the rate of approximately 20 c.c. every 15 minutes, was moderately viscous and opaque with free acid remaining in the neighborhood of 15 units. Abruptly he was asked whether or not his own and his wife's ambitions had been satisfied by his becoming a tugboat engineer. His manner became serious and slightly grim, but he maintained that the work had been entirely satisfactory. He was then asked where a tugboat engineer stood in the social constellation of men who had qualified as chief engineers. His even manner continued although tension was evident by this time and he wiped a tear from each eye. He was further asked about possible conflicts with his wife. He denied conflicts but the denial was associated with additional lacrimation and within one-half hour of the start of this interview the gastric rugae had become intensely red (80) and engorged, completely filling the area of the stoma. Motor activity became intense and sustained and free acid rose to 35 units. No pain was noted.

*Comment.* This experiment provides direct visual confirmation of the findings detailed above in patients with peptic ulcer in whom the contemplation of relevant personal conflicts was associated with intense gastric hyperfunction and often symptoms.

*Nature of the Personality Reaction.* Numerous attempts have been made to explain why some individuals in a setting of significant emotional conflict develop troublesome gastric hyperfunction and perhaps peptic ulcer, while others may develop precisely the opposite changes in the stomach with hyp acidity, slow emptying and nausea and still others develop other physiologic disturbances but no evidence of gastric disorder. Analysis of the conflict situation has not been fruitful, and neither have attempts to construct a constitutional or personality profile been successful in delineating very sharply between those who develop and those who do not develop peptic ulcer. It has been more profitable to examine and characterize the way in which the individual habitually met threats and challenges in his life situation. The subject with peptic ulcer may feel passive and have strong dependent needs as has been pointed out by Alexander<sup>11</sup> and numerous others,<sup>8, 12, 13</sup> but his behavior is aggressive. He must appear master of the situation in contrast to the subject with gastric hypofunction, who readily assumes a passive rôle in human relationships.<sup>14</sup> The gastric hyperfunction itself implies a need to be fed and sustained, but it is an aggressive biologic response which in animals including man precedes the act of devouring. It is thus in keeping with the general behavior reaction of competitive aggression. These features have been reviewed elsewhere.<sup>5, 10, 11</sup> One probably could not answer in simple

5. WOLF, STEWART and WOLFF, H. G.: Human gastric function. An experimental study of a man and his stomach, 2nd ed., 1947, Oxford University Press, New York.
6. PALMER, W. L.: Mechanism of pain in gastric and in duodenal ulcer, *Arch. Int. Med.*, 1927, xxx, 109.
7. WOLF, STEWART and ANDRUS, W. D.: The effect of vagotomy on gastric function, *Gastroenterology*, 1947, viii, 429.
8. SZASZ, T. S., KIRSNER, J. B., LEVIN, E., and PALMER, W. L.: The role of hostility in the pathogenesis of peptic ulcer: Theoretical considerations with the report of a case, *Psychosom. Med.*, 1947, ix, 331.
9. MIRSKY, I. A.: Title at Am. Psychosom. Soc., *Psychosom. Med.* In press.
10. MITTELMANN, B., and WOLFF, H. G.: Emotions and gastroduodenal function, *Psychosom. Med.*, 1942, iv, 5.
11. ALEXANDER, F.: Clinical notes: Treatment of a case of peptic ulcer and personality, *Psychosom. Med.*, 1947, ix, 320.
12. HEIDE, CAREL VAN DER: A study of mechanisms in two cases of peptic ulcer, *Psychosom. Med.*, 1940, ii, 398.
13. DUNBAR, FLANDERS: Emotions and bodily changes, 1946, Columbia University Press, New York.
14. WOLF, STEWART: Observations on the occurrence of nausea among combat soldiers, *Gastroenterology*, 1947, viii, 15.
15. WOLF, STEWART, PFEIFFER, J. B., RIPLEY, H. S., WINTER, O. S., and WOLFF, H. G.: Hypertension as a reaction pattern to stress; summary of experimental data on variations in blood pressure and renal blood flow, *Ann. Int. Med.*, 1948, xxix, 1056.



## CASE REPORTS

*Case 1.* A 43 year old Irish-Hawaiian male was first admitted to Queen's Hospital July 12, 1945, with a chief complaint of weakness. He had diabetes and had been taking insulin "off and on" for one year. During this period he had developed a persistent diarrhea, had lost about 70 pounds, and had become very weak. He described his stools as being large and yellow, with "droplets of oil" on the surface of the water after an evacuation.

His past history included measles, mumps, and chickenpox in childhood, and pneumonia at the age of 27. The only previous gastrointestinal disturbances he had ever experienced were three bouts of severe epigastric pain many years previously, which the patient attributed to over-indulgence in alcohol. His father had had diabetes and died at the age of 54. His mother had died of a "stroke" at the age of 72. There was no other history of diabetes in the family

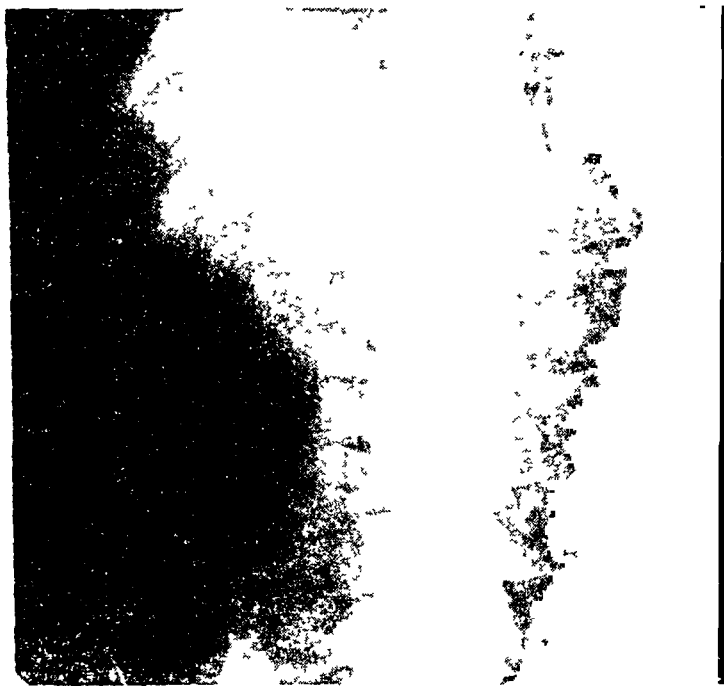


FIG. 1. Roentgen-ray of the abdomen, case 1, showing multiple calcifications in the head and tail of the pancreas.

Physical examination revealed a tall, gaunt male who appeared chronically ill. There were slight reddening and atrophy of the tongue, and tiny fissures at the corners of the mouth. The remainder of the examination was essentially negative except for evidence of rather marked weight loss. Admission blood count showed 5,180,000 erythrocytes, 13 gm. of hemoglobin, and 16,150 leukocytes, with 42 per cent polymorphonuclear leukocytes and 58 per cent lymphocytes. The urinalysis was negative and the blood sugar was 158 mg. per cent. A stool examination showed a large number of striated muscle fibers and 16 per cent of the dry weight was fat.

A barium enema revealed a normal colon but the roentgenologist noted a large accumulation of calcific deposits in the pancreas. A lateral film of the abdomen confirmed the location of the calcifications. An oral cholecystogram demonstrated a normal gall-bladder. An upper gastrointestinal roentgen-ray study was essentially negative except for a slight compression of the descending and transverse portions of the duodenal loop from without, apparently by the head and body of the pancreas.

calcium was 9.4 mg. per cent and the blood phosphorus was 2.8 mg. per cent. The blood Laughlen test was negative. Blood amylase was 10 per cent (Fennel's method: 10 per cent to 35 per cent is normal), and the urinary amylase was 2 per cent. A roentgenogram of the abdomen again demonstrated the multiple pancreatic calcifications, and a chest film showed bronchiectasis of the left lower lobe with an associated pleural reaction obliterating the corresponding diaphragm.

Carbohydrate metabolism was still erratic and great difficulty was encountered in stabilizing his diabetes. As he gained weight, however, his insulin requirement gradually decreased from 110 to 40 units of insulin daily. He was given kaopectate and at times paregoric for his diarrhea, as well as pancreatin, one gram three times daily. Amphogel was effective in relieving the sporadic epigastric pain of which he complained. He improved slowly, the cough disappeared, and his weight increased to 146 pounds. He was discharged April 18, 1946.

*Third Admission.* The patient was readmitted July 10, 1946, with a chief complaint of hemoptysis. He had felt well until about 10 days prior to admission, when he contracted a "cold." He developed a cough productive of yellow sputum which later became blood-tinged. A few moist râles at the left apex were the only new finding on physical examination. The blood count was normal except for a slight leukocytosis (11,200), with a normal differential, and the urinalysis was negative except for a four-plus sugar reaction. The blood sugar was 196 mg. per cent. The sputum contained large numbers of tubercle bacilli, and a chest film demonstrated a small reticulated infiltration in the upper lobe of the right lung. A right phrenicotomy was done September 11, 1946, and one week later the sputum was negative for acid-fast bacilli on three successive examinations. His diabetes remained difficult to control and a day-to-day variation of the insulin dosage was necessary. Steatorrhea was still present but responded fairly well to pancreatin and kaopectate, and his weight increased from 134 to 144 pounds. He was transferred to a sanatorium September 28, 1946.

*Case 2.* A 39 year old white male applied for a position as chef at Queen's Hospital in August, 1946. The preemployment chest roentgenogram showed a moderately large pulmonary infiltration in the apical portion of the left lower lobe, probably tuberculous. He was admitted to the isolation unit of the hospital and put on a regimen of strict bed rest. His history revealed that he had had an increasingly productive cough for about three weeks, but no other symptoms. Physical examination was entirely negative. His blood pressure was 120 mm. Hg systolic over 78 diastolic.

There was nothing of note in his past history up to about two years before admission, at which time he had suffered a marked weight loss (approximately 70 pounds in two months), attributed by the patient to the fact that he had just had most of his teeth extracted. However, a Selective Service examination revealed that he had diabetes mellitus. He was rejected and no treatment was undertaken by the patient. Eighteen months prior to admission he had been hospitalized in Los Angeles with a bilateral pneumonia and during his stay in the hospital treatment of his diabetes was carried out. He was taking 40 units of protamine zinc insulin each morning at the time of discharge, and continued to take it regularly until his admission to Queen's Hospital. Chest roentgen-ray at the time of discharge was said to show complete resolution of the pneumonia. A short time before the patient developed this pneumonia, a close personal friend had died of pulmonary tuberculosis. There was no family history of diabetes or tuberculosis.

The sputum was positive for acid-fast bacilli. The sedimentation rate was not elevated. The blood count was normal and the urinalysis was negative. He was put on a daily dose of 55 units of protamine zinc insulin. His appetite seemed to increase steadily, but on the sixtieth hospital day his weight was the same as on ad-

revealed entirely normal spinal fluid, and an electrocardiogram on the fourth day was essentially normal except for tachycardia. A serum amylase determination on the fourth day was normal, and the serum calcium was 11.4 mg. per cent. Although his white count slowly fell to 18,000, his fever progressively mounted and he died on the fifth day without having regained consciousness. Penicillin, 50,000 units, had been given intramuscularly every two hours since admission. The clinical diagnoses were insulin shock of irreversible type, such as occurs in about 1 per cent of all patients given insulin shock therapy,<sup>7</sup> and bilateral bronchopneumonia.

At autopsy, the pancreas weighed 80 grams and felt like a bag of pebbles. On section, multiple irregular calcific nodules were found throughout, the largest measuring about 0.5 cm. across. The entire gland seemed to consist of dense connective tissue so that no parenchyma could be identified and the ducts could not be made out. Histologic study showed it to be densely fibrotic connective tissue containing only a few islands of Langerhans, a few duct-like structures, and an occasional small nest of distorted acinar cells. The many calcifications seemed to be deposited around what appeared to be areas of old fat necrosis. The islets which remained were small and in the process of being obliterated by the fibrotic process. The liver weighed 1,750 grams and was firm and smooth, with moderate passive congestion, but no fatty infiltration was detected. The gall-bladder appeared normal, emptied easily, and contained no stones. There was no evidence of fat necrosis in the mesentery or omentum. Three small superficial ulcers, which proved to be tuberculous on histologic examination, were found in the mucosa of the ileum near the ileo-cecal valve. Each lung weighed 720 grams and showed mild congestion and edema, with patchy atelectasis and lobular pneumonia. A well walled-off tuberculous abscess, 2 cm. in diameter, was present in the left apex together with a cicatrizing pleural scar. A similar lesion was found at the hilum of the left lung.

### DISCUSSION

The outstanding clinical features of these two cases of pancreatic calcification were: (1) steatorrhea with marked weight loss, (2) severe, and in one case intractable, diabetes, and (3) complicating pulmonary tuberculosis. It has been generally observed that steatorrhea occurs in only about one-half of all cases of calcareous pancreatitis. It was a prominent feature in both cases reported, although only the first patient actually complained of diarrhea. Pancreatic insufficiency could reasonably be expected from the relatively marked destruction of glandular tissue that was shown by the roentgen-ray, although disturbances of pancreatic function have been absent in about 10 per cent of the reported cases of pancreatic calcification.<sup>4</sup>

Diabetes mellitus, latent or active, is said to occur in about 50 per cent of all cases of pancreatic calcification.<sup>8</sup> This is a much higher incidence of diabetes than occurs when pancreatic damage is due to obstruction of the ducts by a pancreatic calculus. It is well known that when stones obstruct the pancreatic ducts, destruction of the acinar tissue is early, rapid, and quite complete, but the islands of Langerhans survive until very late in the process. Exocrine failure precedes endocrine failure of the pancreas when pancreatic destruction is due to ductal obstruction. No better illustration of this could be cited than the fact that Banting and Best were launched on the investigation which ultimately led to the discovery of insulin<sup>9</sup> by Barron's autopsy report on a patient who had had a pancreatic stone.<sup>10</sup> The pancreas of this

metabolic disturbances has been reported. Calcification may rarely develop painlessly (only one case in Comfort's series). Case 2 was evidently in this category.

It should, of course, be borne in mind that acute interstitial and acute hemorrhagic pancreatitis are distinct entities and may occur only once in the lifetime of an individual. That the latter and chronic relapsing pancreatitis are not identical is highlighted by the fact that diabetes has been found only rarely (2 per cent) to follow acute hemorrhagic pancreatitis,<sup>13</sup> whereas it occurs in 50 per cent or more of all cases of calcareous pancreatitis.

Complicating biliary disease is reported to be fairly common in almost all forms of pancreatic disease. A normal cholecystogram was obtained in the first case, and although abnormal function was reported in the second case, no structural abnormality was discovered at autopsy. Degenerative fatty infiltration of the liver producing a palpably enlarged liver occurs in some cases of chronic pancreatitis, the "pancreato-hepatic syndrome,"<sup>14</sup> most probably due to a deficiency in lipocaic, the pancreatic hormone which regulates the deposition of fat in the liver cells. Hepatomegaly was not present in the first case, and the liver was essentially normal on histologic study in the second case.

A history of alcoholism has often been cited as a salient feature in pancreatic inflammatory disease. It was regarded, however, as a merely coincidental finding until the accumulation of recent evidence, which has pointed to alcohol as at least a frequent precipitating agent if not actually of etiological importance. Carter<sup>15</sup> found tremendously elevated serum amylase values in 11 alcoholic patients with acute abdominal symptoms. Four of the patients were operated upon and acute interstitial pancreatitis was found. Alcohol definitely precipitated acute attacks in 14 per cent of Comfort's cases of chronic relapsing pancreatitis, and 59 per cent of his patients were users of alcohol. This has borne out the observations of earlier writers such as Weiner and Tennant,<sup>16</sup> Myers and Keefer,<sup>17</sup> and Clark.<sup>18</sup> Our first patient was a constant heavy user of alcohol, and the second patient was a sporadically heavy drinker. In a study of 4,000 autopsies, Weiner and Tennant concluded that pancreatic disease is 40 to 50 times as frequent among alcoholics as among non-alcoholics.

Patients with calcifying disease of the pancreas are predisposed to pulmonary complications, and both of our cases developed pulmonary tuberculosis. Two of Pasternack's cases and one of Snell and Comfort's also had pulmonary tuberculosis. Other pulmonary complications, such as bronchopneumonia, abscess, and gangrene have been reported. It is interesting to speculate as to whether or not the metaplasia of the bronchial epithelium resulting in these patients from the loss of vitamin A in the fatty stools<sup>13</sup> is an important factor in predisposing them to pulmonary infections. It appears that the pancreatic insufficiency not only predisposes to pulmonary infection but also has quite a direct bearing on the patient's response to it. The first patient had intractable diabetes and showed relatively little resistance to the

common duct to the stomach, duodenum, or jejunum), or external drainage by means of choledochostomy or cholecystostomy. Pain and pressure symptoms arising from pancreatic cysts which sometimes occur in chronic pancreatitis are relieved by marsupialization or internal drainage of the cysts into the small intestines. When intractable pancreatic pain is not demonstrably due to any of the above mentioned factors, more radical surgery may be necessary. Successful subtotal pancreatectomy with complete relief of pain in a small number of such patients has been reported during the past year.<sup>4, 19</sup>

### SUMMARY

1. Two cases of chronic pancreatitis with calcification, diabetes, and steatorrhea are reported.
2. Both cases were complicated by pulmonary tuberculosis.
3. The incidence, classification, pathogenesis, clinical features, and treatment of calcifying pancreatitis are briefly discussed.

### BIBLIOGRAPHY

1. PASCUCCI, L. M.: Pancreatic cyst and lithiasis, *Am. Jr. Roentgenol.*, 1944, lii, 80-87.
2. SNELL, A. M., and COMFORT, M. W.: The incidence and diagnosis of pancreatic lithiasis, *Am. Jr. Digest. Dis.*, 1941, viii, 237-243.
3. GRANEY, C. M., and REDDICK, R. H.: Calcification of the pancreas, *Am. Jr. Surg.*, 1944, lxxv, 271-275.
4. COMFORT, M. W., GAMBILL, E. E., and BAGGENSTOSS, A. H.: Chronic relapsing pancreatitis, *Gastroenterology*, 1946, vi, 239-285 and 376-408.
5. MARSHALL, W. A.: Pancreatic lithiasis, with case report and autopsy findings, *Radiology*, 1938, xxxi, 562-566.
6. FANGER, H.: Pancreatic lithiasis with associated intestinal hemorrhage, *New Eng. Jr. Med.*, 1944, ccxxxi, 678-680.
7. KALINOVSKY, L. B., and HOCH, P. H.: Shock treatments, 1946, Grune and Stratton, New York.
8. PASTERNAK, J. G.: Calcareous pancreatitis, *Ann. Int. Med.*, 1943, xix, 757-767.
9. BANTING, F. G., and BEST, C. H.: The internal secretion of the pancreas, *Jr. Lab. and Clin. Med.*, 1922, vii, 251-266.
10. BARRON, M.: The relation of the islets of Langerhans to diabetes with special reference to cases of pancreatic lithiasis, *Surg., Gynec. and Obst.*, 1920, xxxi, 437-448.
11. ELMAN, R.: Acute interstitial pancreatitis, *Surg., Gynec. and Obst.*, 1933, lvii, 291-309.
12. EDMONDSON, H. A., and FIELDS, I. A.: Relation of calcium and lipids to acute pancreatic necrosis, *Arch. Int. Med.*, 1942, lxxiv, 177-190.
13. ELMAN, R., and SACHAR, L. A.: Contributions made in 1940 to knowledge in regard to the pancreas, *Am. Jr. Digest. Dis.*, 1941, viii, 105-112.
14. ELMAN, R., and AKIN, J. T.: *Gastroenterology*, 1944, ii, 412-426.
15. CARTER, S. J.: Serum amylase findings in chronic alcoholic patients with acute, severe abdominal symptoms, *Ann. Surg.*, 1945, cxxii, 117-121.
16. WEINER, H. A., and TENNANT, R.: A statistical study of acute hemorrhagic pancreatitis, *Am. Jr. Med. Sci.*, 1938, cxcvi, 167-176.
17. MYERS, W. K., and KEEFER, C. S.: Acute pancreatic necrosis in acute and chronic alcoholism, *New Eng. Jr. Med.*, 1934, ccx, 1376-1380.
18. CLARK, E.: Pancreatitis in acute and chronic alcoholism, *Am. Jr. Digest. Dis.*, 1942, ix, 428-431.

# A SURVEY OF THE ACTUALITIES AND POTENTIALITIES OF EXFOLIATIVE CYTOLOGY IN CANCER DIAGNOSIS \*

By GEORGE N. PAPANICOLAOU, M.D., *New York, N. Y.*

IN 1925, when for the first time I had occasion to discuss with the late Dr. James Ewing, then Professor of Pathology in our School at Cornell, the possibility of using the vaginal smear as an aid in the diagnosis of uterine cancer, he asked me whether this method could be applied to endometrial as well as to cervical carcinomas. It was his opinion that such a method might prove to be of greater value in the diagnosis of adenocarcinomas of the endometrium than in carcinomas of the cervix, for which everyone would most likely resort to the well established and more dependable method of biopsy.

At that time my knowledge of the cytologic method was very limited and I was in no position to state whether a differential diagnosis between carcinomas of the cervix and adenocarcinomas of the fundus on a cytologic basis was possible. Nor did I know then that the diagnosis of carcinomas of the cervix by the smear method would be possible at an early asymptomatic stage, making it useful in detecting unsuspected lesions, which might still be invisible.

Now that the method has been tested by general use over a number of years our knowledge has been advanced to a point where we are able to differentiate with a fair degree of accuracy between lesions affecting different parts of the female genital tract, as well as between various cell types and smear patterns. We are now in a position to make a clearer distinction between the squamous cell type carcinomas of the cervix and the adenocarcinomas of the endometrium, in which the abnormal cells are of the glandular type. It is even possible at times to make a differentiation between an adenocarcinoma of the endometrium and one of the cervix, in which the abnormal cells are of the endocervical type.

Metaplasias of the endocervix and of the endometrium may also be recognized occasionally when clusters of endocervical or endometrial cells are present, in which some of the cells show a change toward the parabasal squamous type. In metaplasia of the endometrium one often encounters rosette-like clusters of cells in which there is marked enlargement and vacuolization of some of the more peripherally located cells. Endocervical or endometrial polypoid hyperplasias may be revealed by small polypoid fragments of the endocervical or endometrial mucosa found in endocervical or endometrial smears.

\* Presented as a Morning Lecture, Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 30, 1949.

The original work referred to in this paper has been aided by the Commonwealth Fund and by the National Cancer Institute.

From Cornell University Medical College.

The term "dyskaryosis" has been adopted to designate these early cytologic changes, which are centered in the nucleus. Several types of dyskaryosis may be distinguished on the basis of a predominance of one or more distinctive cell types.

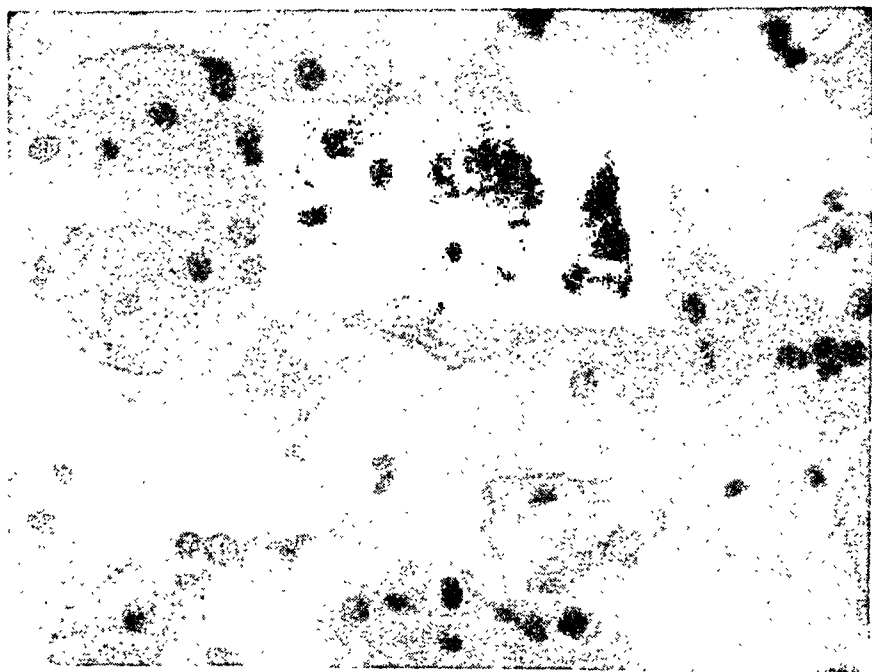


FIG. 1, a. Superficial squamous cells. Normal.  $\times 400$ .

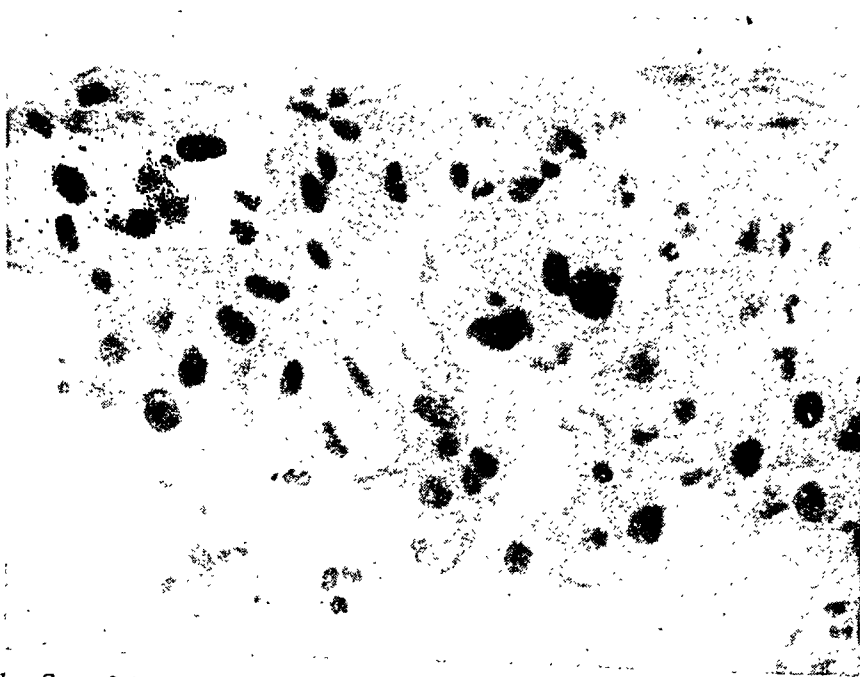


FIG. 1, b. Superficial squamous cells characteristic of superficial cell dyskaryosis.  $\times 400$ .

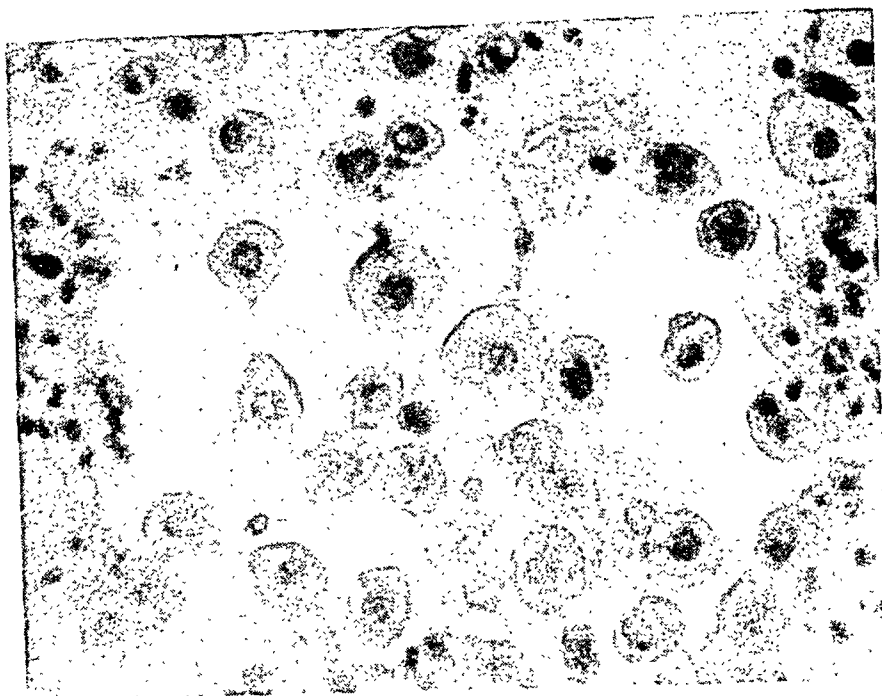


FIG. 3, *a*. Cervical parabasal cells. Normal.  $\times 400$ .

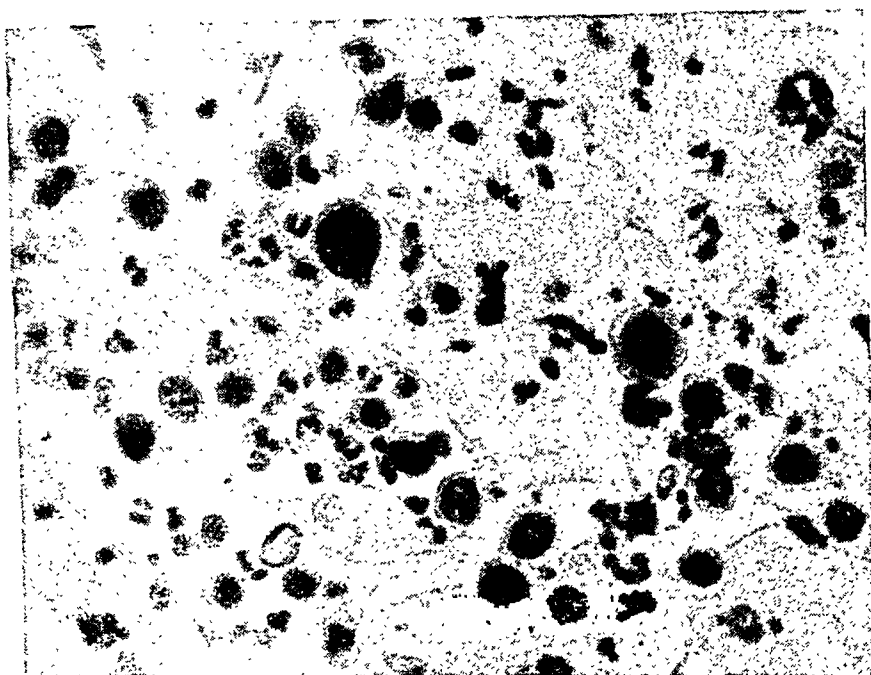


FIG. 3, *b*. Cervical parabasal cells characteristic of parabasal cell dyskaryosis.  $\times 400$ .

The term "intermediate or navicular cell dyskaryosis" is used to indicate the prevalence of abnormal cells deriving from the intermediate or navicular zone (figures 2a, 2b). This type of dyskaryosis is rather rare and thus far we have had only two clear-cut cases of it.



The significance and the prognostic value of these different patterns which seem to correspond to the earliest stages of malignant lesions of the cervix are not yet properly understood, nor will they be until an exhaustive correlative study of cytologic and pathologic findings has been made. What tends to complicate the picture is that not infrequently cells representing various dyskaryosis types are found to be intermixed.

Cases have also been noted in which the dyskaryotic cytology was found to coexist with that of an invasive squamous cell carcinoma. In some of these cases transitional cell forms linking the two cytologic patterns have also been observed. Should this fact be interpreted as indicating that the one would eventually develop into the other? An affirmative answer would be only an assumption, since in none of these cases have we had any positive evidence of a progressive change from one pattern to the other. On the other hand, in at least one case of superficial cell dyskaryosis, which we followed over a period of 10 years, this condition proved to be reversible.

Our observations in this field of early malignant lesions of the cervix and of their corresponding cytologic patterns are still fragmentary. It is not always possible to obtain a confirmation of smear findings by biopsy. Instances are not uncommon in which multiple biopsies have been necessary to prove the presence of an early carcinoma. In a recent case, only one out of eight biopsies taken offered positive evidence of a carcinoma in situ. Even after complete hysterectomy it is not possible to verify the absence of a malignant lesion without a serial microscopic study of the cervix, which is impracticable as a routine procedure.

Another difficulty is the lack of general agreement among pathologists as to the criteria of a carcinoma in situ. It sometimes happens that a section showing a marked degree of epidermidalization may be interpreted in some laboratories as carcinoma in situ. All these reasons make it very difficult to evaluate accurately the incidence of carcinoma in cases in which a dyskaryosis smear pattern has been observed.

In view of the fact that at present no general agreement can be reached as to the criteria of carcinomas in situ, their separation into two groups appears to be justifiable. One of the two groups would include cases characterized by clean-cut criteria that would be generally acceptable and that would satisfy the most exacting standards; the other would consist of cases in which the criteria fall below such standards and in which there may be disagreement as to the true nature of the lesion.

The term "carcinoma in situ" or "intraepithelial carcinoma" should be retained for the first group, whereas the second one should be designated by a new term which would not necessarily suggest malignancy. The term "pre-cancerous", which has been used extensively for ambiguous lesions, would be rather objectionable, as it implies an inevitable malignant transformation. In a recent discussion of this point the term "dysplasia" \* was

\* This term was suggested by Dr. William B. Ober of the National Cancer Institute at Bethesda, Maryland.

of the malignant cells, their extreme hyperchromasia, the anisokaryosis and the scantiness of the cytoplasm.

Adenocarcinomas may be recognized as such when the cells are well preserved and reveal their glandular origin. Exfoliated cells of this type frequently show an eccentric position of the nucleus and vacuolization of the cytoplasm. The cells are often grouped in rosette-like clusters.

Malignant neoplasms of lymphoid origin, such as Hodgkin's disease or reticulum-cell sarcoma, also present a distinct cytologic picture. The cells appear, as a rule, singly, and although relatively small, they can be safely identified by the coarse granulation, hyperchromasia, and fragmentation of their nuclei. An excess of lymphocytes was observed in some cases of lymphatic leukemia. In general, it may be stated that large clusters of lymphocytic cells in sputum or bronchial washings appear to be almost invariably associated with malignant neoplasms.

Another group of neoplasms of the lungs which show good exfoliation and can be detected by the examination of sputum or bronchial washings is that of the alveolar cell carcinomas. A cytologic feature which may help in the recognition of this type is the not infrequent presence of multinucleated cells of a rather characteristic appearance.

Of the non-malignant conditions, one which may occasionally display a distinctive cytology is bronchiectasis. Clusters of atypical cells which are sometimes found in this condition show considerable resemblance to clusters of neoplastic cells. The normal structure and the uniformity of their nuclei are a help in interpreting them correctly.

In our laboratory we attribute equal importance to the examination of sputum and to that of bronchial aspirates and washings. We have had instances of positive cases in which the sputum was negative and the bronchial washing positive, but other cases in which the contrary was true. When findings are negative at least three specimens should be examined.

In order to secure a good preservation of the cells we fix the sputum specimens in 70 per cent alcohol as soon as collected. The bronchial washings are mixed immediately with 95 per cent alcohol and then centrifuged. Smears prepared from the sputum, as well as those prepared from the sediment of the bronchial washings, are fixed again in alcohol-ether and stained by our standard smear-staining procedure which insures a good differentiation between basophilic and acidophilic cells. This differentiation is most important for the detection of the acidophilic and orangeophilic cells which are a characteristic feature of the squamous cell carcinomas.

In the urinary tract the most successful application has been in carcinomas of the bladder. As a rule, carcinomas of this organ exfoliate copiously and the cells usually appear in clusters showing structural abnormalities which reveal their malignant nature. In two instances an unsuspected carcinoma, concealed in a diverticulum of the bladder, has been detected by the use of the smear technic.

very scanty. The specific cytology of various types of tumors of the kidney still needs further clarification. Special methods of staining may eventually be found to be necessary for the identification of some of these types.

The administration of estrogens causes marked changes in the epithelium of some of the organs of the urinary tract. As a rule, these changes are reflected in the smears.- Both the transitional epithelium of the bladder and the glandular epithelium of the prostate may show cellular and nuclear enlargement and an increased production of glycogen as the result of a prolonged estrogenic therapy. Some of the superficial transitional cells change to a type resembling that of the cornified small-nucleated acidophilic squamous cells found in the vaginal secretion.

It is of interest that a prolonged administration of estrogens in prostatic carcinomas may cause an enlargement not only of the normal but also of the cancer cells, thus greatly facilitating their recognition in the smears. It is, therefore, likely that the use of estrogen therapy prior to the smear examination will tend to increase exfoliation and to cause cytologic changes that would help in the identification of exfoliated cancer cells. Such a use of estrogens has been proved to be of value in carcinomas of the female genital organs.

With regard to the matter of obtaining suitable urine specimens it may be stated in general that catheterized specimens are preferable to voided, more necessarily in women because of the admixture of vaginal cells in voided urine. The types of urine specimens required for the diagnosis of lesions of the prostate or of the ureter and kidney have already been mentioned.

The urine is mixed with an equal amount of 95 per cent alcohol as soon as collected.\* It is subsequently centrifuged, and smears prepared from the sediment are fixed again in an alcohol-ether solution and then stained by the same method used for other smears.

Special difficulties are encountered in the use of the smear method for the diagnosis of gastric carcinomas. Of these the two most important are the relatively rapid deterioration of exfoliated cells in the gastric fluid and the continual emptying of the gastric contents into the intestines, which does not allow a sufficiently large accumulation of exfoliated cells within the stomach. Another adverse factor is the rather frequent presence of extraneous cells in the gastric fluid. Clusters of cells from the nasal and bronchial mucosa and dust cells are those apt to be the most troublesome.

Despite these drawbacks the cytologic method is of recognized value in the diagnosis of gastric carcinomas. By improving our cytologic criteria and our technical procedures we hope to bring this application up to much higher standards, although the percentage of false negatives will most likely remain higher in this than in other applications.

\* The procedure of fixing specimens immediately and prior to centrifugation by mixing them with equal amounts of 95 per cent alcohol applies to all fluids with the exception of pleural and peritoneal fluids. These are mixed with equal amounts of 50 per cent alcohol, as the 95 per cent alcohol causes a much greater coagulation of proteins, which tends to reduce the amount of sediment.

As far as actual results are concerned it may be safely stated that certain applications, such as those of the female genital tract and of the respiratory tract, have been advanced to a point where they can now be used in routine laboratory diagnosis. There is an increasing number of publications dealing with the practical advantages and disadvantages of the method and giving an estimate of its dependability as a diagnostic procedure. Although the results obtained by investigators in different laboratories are at variance in some respects, they do permit one to arrive at certain conclusions, in which there is more or less general agreement.

One important point on which there is evidence of such an agreement is that the cytologic method is not to be considered as a method of final diagnosis and that confirmation of smear findings by biopsy or curettage is indicated wherever possible.

On the other hand, it is generally conceded, even by those who are most skeptically inclined, that this method is of unquestionable value in the detection of early or unsuspected carcinomas of certain organs, and is, therefore, particularly adapted to screening purposes. It is also highly useful in evaluating the effects and in following up the results of irradiation or other therapy.

With regard to the diagnostic accuracy of the method, it would be very difficult to make an overall statistical evaluation which would apply to all groups. Figures given out by various investigators show considerable variation. What we are striving for in our laboratory is to limit to a minimum the percentage of false positives. We feel that an accuracy of over 95 per cent can and should be maintained in the cases reported as Class IV and of over 98 per cent in those reported as Class V.\* Anything below these figures would not be at all satisfactory, more particularly in the Class V group, in which reports are often used as the basis of a decision for a major operation. Negative reports, as a rule, show a higher percentage of errors, ranging from 5 or 10 per cent, in well explored gynecological cases, to 25 per cent or even more in other applications, more specifically in the gastric.

Some of the drawbacks of the cytologic method are that it is time consuming and that it requires special study even on the part of men with a good pathological background. These disadvantages constitute a serious obstacle to the incorporation of the method in many laboratories and will, no doubt, greatly retard its more widespread adoption. What is more discouraging is the fact that in some laboratories, because of an increasing demand, the method is introduced prematurely, and is put into practice by men who have

\* Classification of reports on smears as applied to the diagnosis of malignant neoplasms

Class		
I	Negative	Absence of atypical or abnormal cells
II	Negative	Atypical cells present but without abnormal features
III	Suspicious	Cells with abnormal features suggestive of but not conclusive for malignancy
IV	Positive	Cells and cell clusters fairly conclusive for malignancy
V	Positive	Cells and cell clusters conclusive for malignancy

# CASE REPORTS

---

## ELECTROCARDIOGRAPHIC CHANGES IN A CASE OF WERNICKE'S SYNDROME \*

By LEON WALLACE, M.D., *Beverly Hills, California*, and  
EUGENE CLARK, M.D., *New York, N. Y.*

It is well known that the heart may be involved and that electrocardiographic changes are found in conditions due to deficiency of the vitamin B complex. This has been shown to occur in beriberi and pellagra.<sup>1, 2, 3, 4, 5, 6, 7, 8</sup> The following case is of interest because of the occult cardiac involvement with striking electrocardiographic abnormalities, which disappeared rapidly after thiamine chloride therapy, in a patient with Wernicke's syndrome (hemorrhagic polioencephalitis superior), a state which clinical and experimental evidence holds ascribable to thiamine deficiency.<sup>9, 10, 11, 12</sup>

### CASE REPORT

A 40 year old white man entered the hospital in a confused state. He was disoriented as to time and place, confabulated, and frequently contradictory. The only history which appeared to be reliable was the admission of chronic alcoholism for at least six years, accompanied by a grossly inadequate food intake. Diplopia of 24 hours' duration was admitted to be present; headache was denied. A questionable history of peptic ulcer was given. No history of heart disease was obtained.

At the time of admission the following physical findings were present: Temperature 99.2° F., pulse 150, respirations 20, blood pressure 114 mm. Hg systolic and 80 mm. diastolic.

The head showed no evidence of injury. The pupils reacted to light and accommodation, and were round, regular and equal. There was left external rectus palsy with diplopia; horizontal, but no vertical nystagmus. The fundi were normal. The ears, nose, mouth, throat and neck were essentially normal.

The lungs were clear to auscultation and percussion. The heart was not enlarged. The sounds were of good quality and regular. Sinus tachycardia was present. There were no murmurs or thrills.

The abdomen was flat and slightly tender in the right upper quadrant. The kidney, spleen and liver were not palpable. Genitalia were normal. The extremities revealed slight cyanosis of both feet and hands.

*Neurological examination:* Deep tendon reflexes were normal in the upper extremities, absent in the lower extremities. The Babinski reaction was equivocal, and plantar hyperesthesia was present.

*Laboratory findings:* White blood count 4850; neutrophils 60 per cent, lymphocytes 33 per cent, mononuclears 2 per cent, eosinophiles 2 per cent, basophiles 3 per cent. Red blood count 4,870,000; hemoglobin 14.5 gm. The Wassermann reaction was negative. Sodium: 312 mg./100 c.c. Non-protein nitrogen: 32 mg./100 c.c.

\* Received for publication November 15, 1946.

From the Third (New York University) Medical Division of Bellevue Hospital, and the Department of Medicine of the New York University College of Medicine.

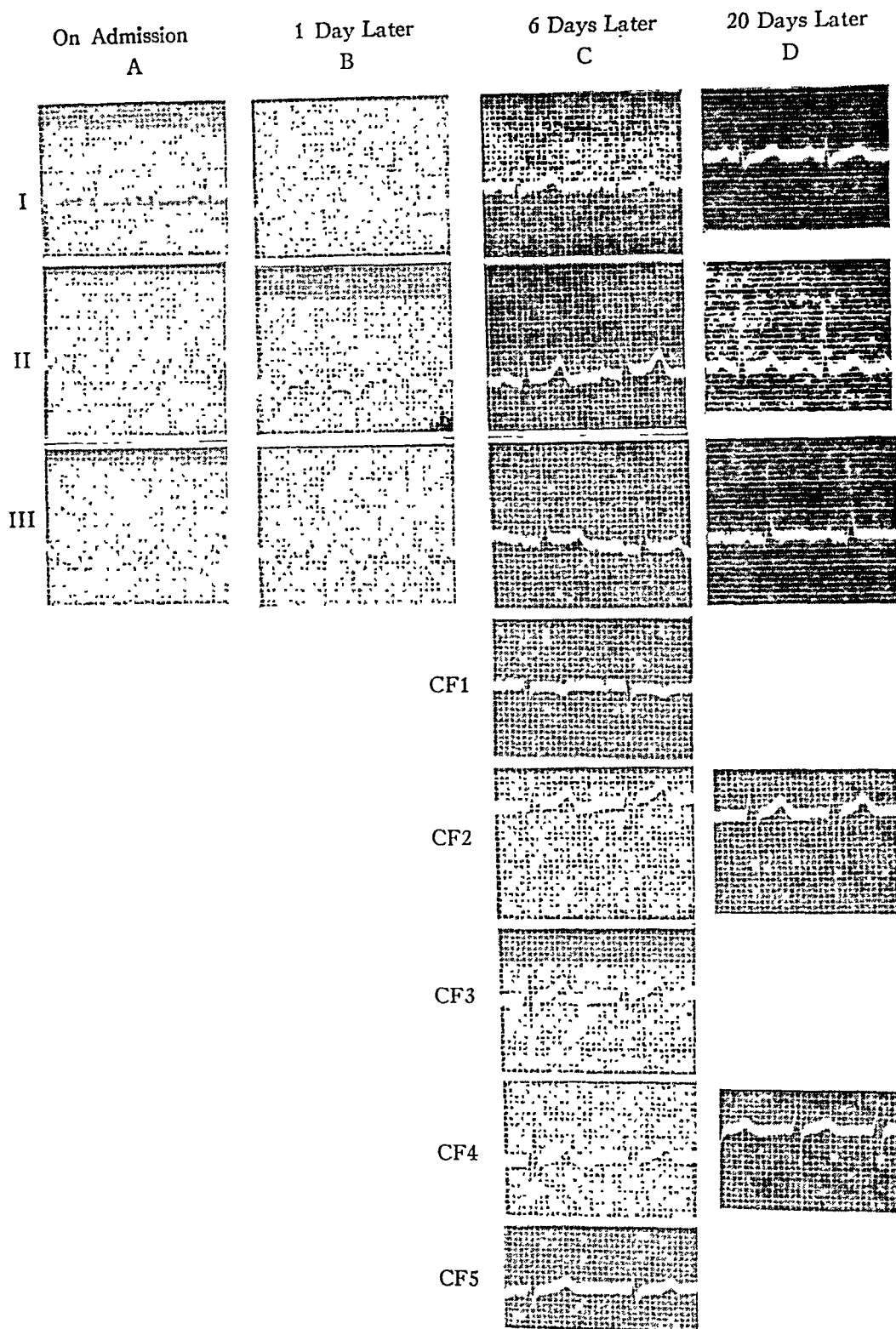


FIG. 1. *A.* On day of admission. Sinus tachycardia of 140. The abnormalities are the low T in Lead I and the inverted T in Leads II and III. *B.* One day later. Sinus tachycardia of 107. The low T in Lead I and the inverted T in Leads II and III persist. *C.* Six days later. Sinus rhythm of 83. The abnormal T waves are now normal as is the entire record. *D.* Twenty days later. Sinus tachycardia of 107. Normal record. The timer was not working while the first three leads were taken.

edge, has as yet appeared in the literature concerning its use in acute infectious mononucleosis. Because of the highly favorable results obtained with it in some viral diseases, it was deemed advisable to try aureomycin\* in a patient with this disease.

#### CASE REPORT

A white female, age 17, became ill on December 29, 1948 with malaise and slight fever. On the following day, she developed a sore throat and when she was first seen at her home on December 31, her temperature was 102° F. Examination at that time revealed the presence of a yellowish-white exudate on both faucial tonsillar stubs as well as on discrete lymphoid tissue deposits on each postero-lateral pharyngeal wall. The exudate assumed a follicular distribution. On either side of the neck, below the angle of the mandible, a solitary lymph node was enlarged and tender but no other lymph glands were palpable. She was given 300,000 units of penicillin in oil intramuscularly that day and on each of the next five days, a total of 1,800,000 units, without any beneficial effect on the course of the illness. Her temperature continued, fluctuating between 100.5° F. and 102° F. until January 4, 1949 and between 102° F. and 104.5° F. until January 7. The exudate, originally in a follicular pattern, now assumed a membranous appearance, involving not only the original sites, but the base of the tongue and the hypopharynx as well. The nasopharynx could not be seen but the clinical condition suggested involvement there, too. She developed a moderate cough with pain in the upper retro-sternal region. On January 5, the eighth day of the disease, the spleen was palpable. The submaxillary glands originally involved remained unchanged but a posterior cervical gland on either side became enlarged and tender. The patient was obviously quite toxic.

A blood count on the seventh day of illness revealed: hemoglobin, 16.7 gm. (104 per cent); red blood cells, 5,100,000; white blood cells, 9200 with a differential count of 33 per cent polymorphonuclear neutrophils, 65 per cent small lymphocytes and 2 per cent monocytes. The serum of blood taken the same day for heterophile antibody determination gave a positive agglutination in a dilution of 1:1792. Two throat cultures during the first six days were sterile for the diphtheria bacillus, positive for *Staphylococcus aureus* and gram negative diplococci.

Aureomycin was started orally at 1 p.m. on the tenth day of the disease on the morning of which the temperature reached 104.5° F. One hour before therapy was begun, however, the temperature dropped to 102° F. After 2.75 gm. were administered during the first 24 hours, the temperature dropped to 98.8° F. (figure 1). She received 2 gm. during the next 24 hours, her temperature varying between 98.8° F. and 100.5° F. After having had 3.75 gm. she developed some nausea and, on one occasion, vomited. The nausea, of slight degree, persisted for about 36 hours when she had two loose bowel movements. The dose for the third day, therefore, was reduced to 1.5 gm., a similar dose being given on the fourth day. The temperature assumed a normal level on the third day, there being no subsequent rise. A final dose of 1 gm was given on the fifth day, making a total of 8.75 gm.

Twenty-four hours after treatment was begun, the patient no longer appeared toxic although she still had considerable dysphagia; the cough and retro-sternal distress disappeared; the spleen was no longer palpable; the enlargement and tenderness of the cervical glands were unequivocally less, reaching a normal state 96 hours after therapy was started. No other glands became palpable. There was no change in the pharyngeal exudate until 48 hours after the drug was begun, at which time several of the lesions began to shrink at their periphery and the dysphagia was minimal. Three days later, the throat was entirely clear.

\*Aureomycin was obtained through the courtesy of Lederle Laboratories Division, American Cyanamid Company.

case reported here might well fit into that category and it may well be that the normal course of this patient's illness would have been prolonged. In this case, it is noteworthy that, coincident with the use of aureomycin, the following changes in the clinical course of the disease occurred within 24 hours:

1. A significant drop in temperature.
2. The spleen was no longer palpable.
3. The patient became markedly less toxic.
4. There was definite diminution in the swelling and tenderness of the cervical lymph nodes.

These observations warrant further clinical trial of aureomycin in infectious mononucleosis.

#### BIBLIOGRAPHY

1. DUGGAR, B. M.: Introductory paper, in Conference on Aureomycin—A New Antibiotic, New York Academy of Sciences, Section of Biology, July 21, 1948.
2. WONG, S. C., and COX, H. R.: Action of aureomycin against experimental rickettsial and viral infections, *Ann. N. Y. Acad. Sci.*, 1948, li, 290-303.
3. BRYER, M. S., SCHOENBACH, E. G., CHANDLER, C. A., BLISS, E. A., and LONG, P. H.: Aureomycin—experimental and clinical investigations, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 117-119.
4. FINLAND, M., COLLINS, H. S., and PAIN, T. F.: Aureomycin—a new antibiotic, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 946-949.
5. WRIGHT, L. T., SANDERS, M. S., LOGAN, M. A., PRIGOT, A., and HILL, L. M.: Aureomycin—a new antibiotic with virucidal properties, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 408-412.
6. SPINK, W. W., BRAUDE, A. I., CASTANEDA, M. R., and GOYTIA, R. S.: Aureomycin therapy in human brucellosis, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 1145-1148.
7. SCHOENBACH, E. B., BRYER, M. S., and LONG, P. H.: The pharmacology and clinical trial of aureomycin: a preliminary report, *Ann. N. Y. Acad. Sci.*, 1948, li, 267-279.
8. BRALEY, A. E., and SANDERS, M.: Aureomycin in ocular infections, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 426-427.
9. MCKINLEY, C. A., and DOWNEY, H.: *Oxford medicine (Christian)*, 1944, v, 498

---

### **HYPERTROPHIC OSTEOARTHROPATHY; REPORT OF A CASE ASSOCIATED WITH A CHORDOMA OF THE BASE OF THE SKULL AND LYMPHANGITIC PULMONARY METASTASES \***

By NATHANIEL UHR, Lt. Col., Medical Corps, A.U.S., F.A.C.P., and  
JACOB CHURG, Captain Medical Corps, A.U.S.,  
*Topeka, Kansas*

MUCH knowledge regarding the clinical aspects of hypertrophic osteoarthropathy has been acquired in the past half century. Its etiology and mechanism, however, remain to be elucidated. In the majority of cases, osteoarthropathy, with its concomitant clubbing of the fingers and toes, is seen as a sequel of chronic suppurative or neoplastic disease of the thoracic organs, less commonly

\* Received for publication May 31, 1946.



but the testicles were much smaller than usual. Studies of ocular fundi disclosed slight papilledema with tortuosity of the veins, more marked on the left. These changes became more pronounced on subsequent examinations. Neurological examination one week after admission revealed exaggerated patellar and Achilles tendon reflexes, the sign of Babinski on the right and a questionable response on the left. Position sense was absent on the right and impaired on the left. Diplopia was noted when the object was at the extreme left; this became progressively more marked within the next two weeks. Bronchoscopy was attempted, but could not be performed because of trismus.

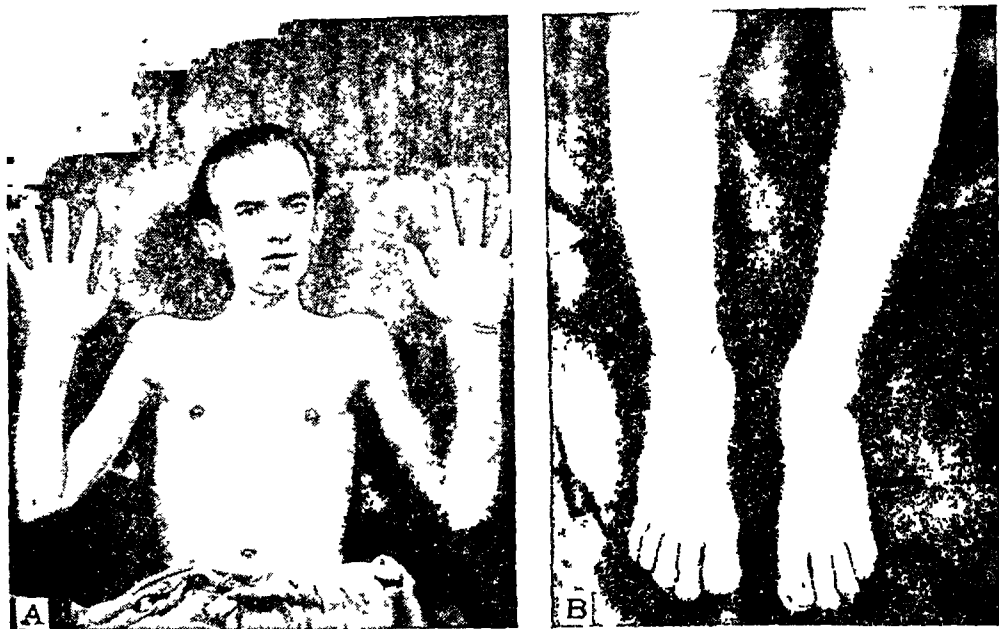


FIG. 1. *a* and *b*. Appearance of patient three weeks before death. Note thickening of forearms and legs.

The subsequent course in the hospital was dominated by increasing clinical and roentgenographic signs of pulmonary involvement. The patient developed cough with moderate expectoration. Rapidly increasing signs of infiltration of the right lung and pleural effusion were followed by similar involvement on the left. The periosteal changes became extremely marked (figure 2, *a* and *b*) and extended to the distal ends of the femora and humeri. Atrophy occurred about the joints. Roentgenograms of the skull revealed marked osteoporosis of the sella turcica with some erosion of the floor and the posterior clinoid processes (figure 2, *d*). The sedimentation rate was persistently elevated up to 52 mm. per hour. The blood calcium was 11.7 mg. per cent, phosphorus 4.2 mg. per cent, alkaline phosphatase 5.9 Bodansky units; white blood count and differential were within normal limits; red blood count was between 4.0 and 3.6 million, with hemoglobin between 12 and 10.8 grams per cent. During the last few days before death fever increased, with irregular elevations up to 103° F. Progressive embarrassment of respiration with cyanosis occurred and was followed by coma and death on July 14, 1944, approximately six months after the onset of symptoms.

*Autopsy.* The autopsy was performed eight hours after death. Only pertinent findings are recorded.

*Gross Examination.* *Skull:* The bones of the skull cut with usual resistance. The meninges were smooth, the subarachnoid fluid clear and colorless and not increased in amount. The vessels of the brain were markedly injected. The base of the

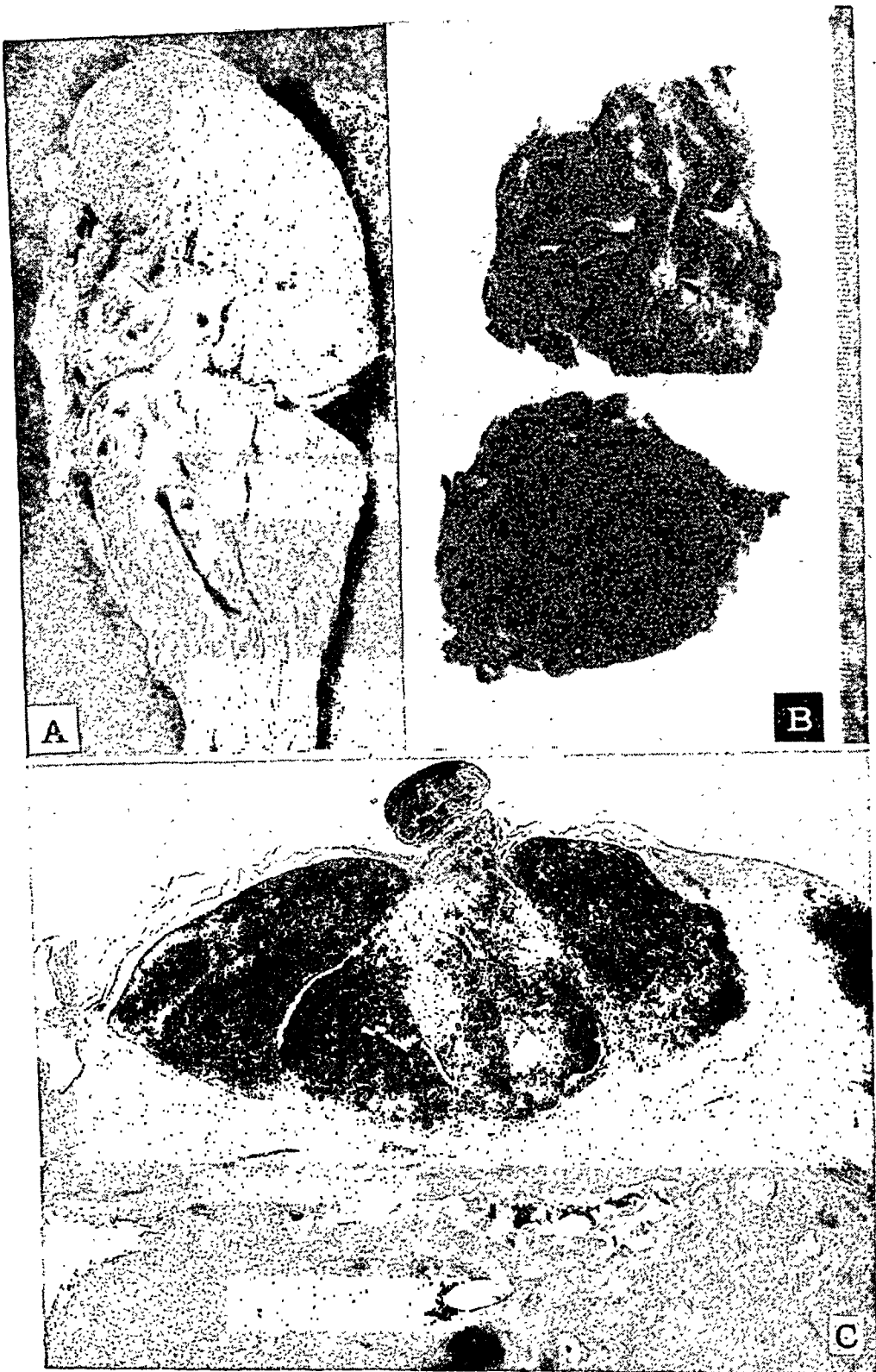


FIG. 3. *a*: Section of the right lung showing peribronchial and perivascular spread of the tumor. *b*: Tumor at the base of the skull and roof of the nasopharynx. *c*: Relation of the tumor to the pituitary gland. Note complete destruction of the sella turcica and the few remaining bony trabeculae within the tumor ( $\times 10$ ).

the gland were well preserved, the majority having distinctly eosinophilic cytoplasm. Along the periphery of the gland were several small areas of necrosis.

*Lungs:* Sections from various parts of the lungs showed a similar microscopic picture. The perivascular, peribronchial and subpleural lymphatics were markedly

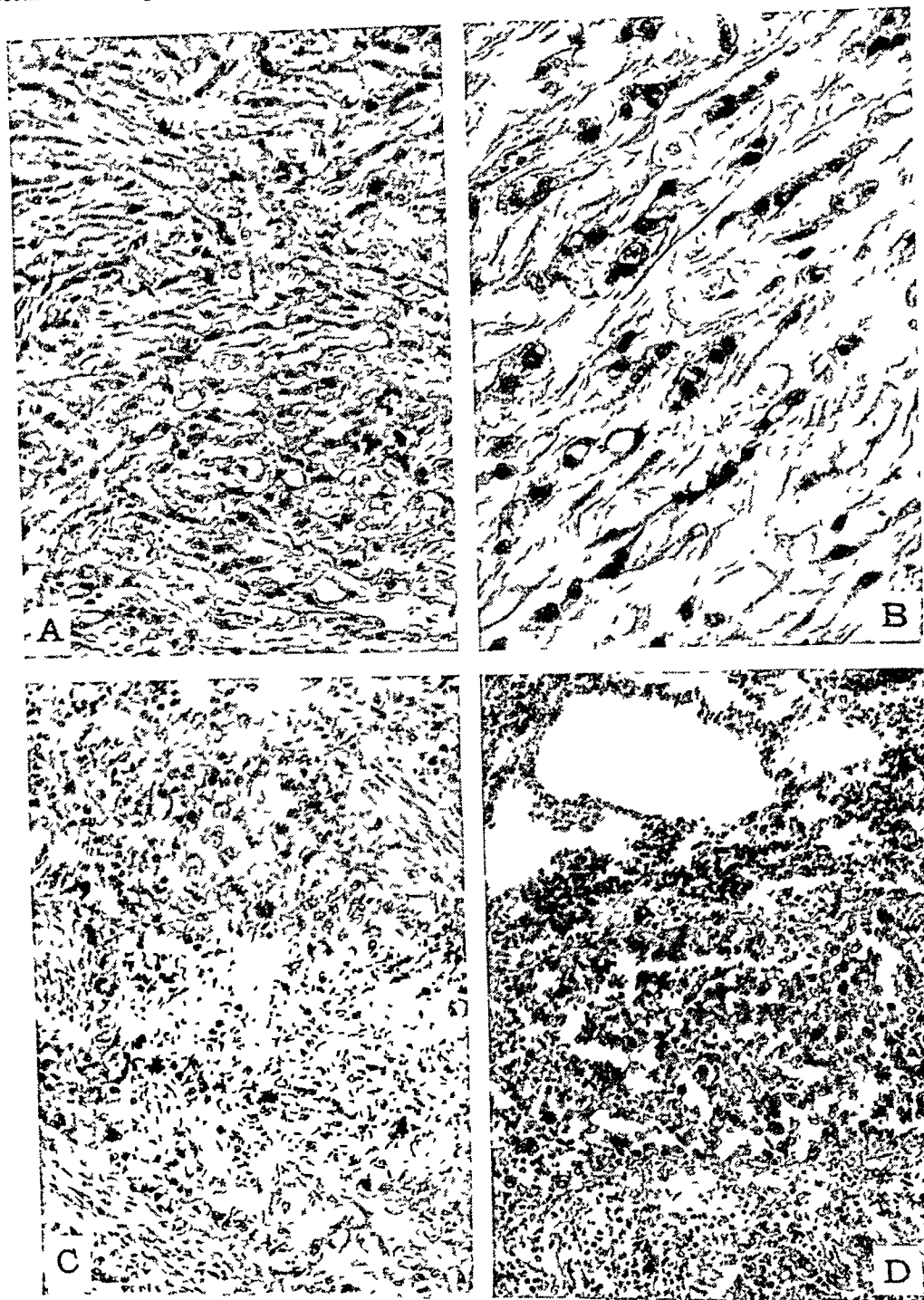


FIG. 4. *a* and *b*: Tumor at the base of the skull showing syncytial meshwork of elongated and stellate cells, "signet ring" cells and the faintly fibrillar, transparent intercellular substance (*A* -  $\times 180$ ; *B* -  $\times 350$ ). *c*: Tumor invading the roof of the nasopharynx. Variation in appearance of cells ( $\times 180$ ). *d*: Tumor cells in a pulmonary lymphatic ( $\times 160$ ).

clear leukocytes intermixed with the tumor cells. In some areas the neoplasm appeared to break out of the lymphatics and infiltrate the adjoining parenchyma and the walls of the smaller blood vessels and bronchi. At one point, in the right main bronchus, the tumor had actually reached the lumen. The parenchyma especially in the right lower lobe was compressed and atelectatic; many alveoli contained edema fluid and polymorphonuclear leukocytes; others were filled with tumor cells. Occasional small blood vessels were occluded by fibrin thrombi.

*Pleura:* The pleura was markedly thickened by masses of tumor tissue, reproducing the structure of the tumor in the base of the skull. Small areas of elongated cells mixed with considerable mucinous intercellular substance, alternated in an irregular fashion with large areas of dense ground substance containing nests of cuboidal cells arranged about small empty spaces. There was a fair number of "signet ring" cells and also many elongated cells resembling fibroblasts. Areas of necrosis were fairly numerous.

*Para-aortic lymph node:* The lymphoid tissue was almost completely replaced by the tumor exhibiting the same pattern as in the pleural metastases. Some of the sinusoids and many of the lymphatics in the immediate vicinity were filled by syncytial masses of cells as seen in the pulmonary lymphatics.

*Testis:* Tubules were well developed but showed incomplete spermatogenesis.

*Fibula.* The original structure of the bone was well preserved, though widening of many of the Haversian canals suggested resorption. The marrow cavity was filled with fat. Superimposed upon the original cortex was a thick irregular meshwork of newly formed trabeculae, covered by thickened periosteum (figure 5, b). The intertrabecular spaces were filled with loose connective or fatty tissue containing occasional clumps of small round cells.

#### COMMENT

The autopsy confirmed the clinical impression of extensive neoplastic involvement of the lungs, and massive hypertrophic osteoarthropathy. The changes at the base of the skull were caused by a malignant tumor identical in structure with that found in the chest. The involvement of the lungs was of "lymphangitic" variety with only secondary infiltration of the parenchyma, bronchial walls and blood vessels. There was no particular area which could have been designated as the primary focus. This fact argued against primary pulmonary neoplasm with metastases to the base of the skull. Reconsideration of the clinical course and detailed histological studies led us to believe that the converse, in fact, was true, that the tumor originated within the base of the skull and metastasized to the lungs and pleura.

The microscopic structure was characterized by the presence of fairly large elongated and polygonal cells with varying amounts of eosinophilic cytoplasm, often containing large vacuoles, and by abundance, in some areas, of clear intercellular mucinous substance. Though the typical "physaliferous" cells are missing, the polymorphous appearance with syncytial-like structure, vacuolization of the cytoplasm, accumulation of intercellular mucinous substance and tendency to arrangement around clear spaces, strongly suggest the diagnosis of chordoma. The topography of the tumor, the location of the most differentiated areas beneath the sella turcica, and the expansion of the involved bones testifies to the intraosseous origin of the growth. These features also help to exclude other tumors at the base of the skull, such as lympho-epithelioma and transitional cell carcinoma of the nasopharynx or sphenoid sinuses. The subsellar, intrasphenoid

of pulmonary neoplasm with hypertrophic osteoarthropathy, emphasized the similarity of certain aspects of this condition to acromegaly, and suggested dyspituitarism as a probable cause. This hypothesis was supported in his cases by acromegalic features, atrophy of testes and gynecomastia in the male, hirsutism and secondary male characteristics in the female, and also by hyperplasia of eosinophilic elements in the pituitary gland. In our case, except possibly for testicular atrophy, no evidence of endocrine dysfunction was observed, yet the pituitary gland showed distinct increase of eosinophilic cells in areas not involved by the tumor. More clinical observations and pathological data are required to establish the rôle of the endocrine apparatus and particularly the pituitary gland in hypertrophic osteoarthropathy. Until then, this theory must be considered an interesting but unproved possibility.

### SUMMARY

1. A case of chordoma at the base of the skull is reported.
2. It is characterized by a high degree of malignancy, unusual for chordoma, by lymphangitic pulmonary metastases, and by early and massive hypertrophic osteoarthropathy.

We offer grateful acknowledgment for the assistance and suggestions given by Drs. S. B. Wolbach and Thomas D. Kinney and Dr. Sadao Otani.

### BIBLIOGRAPHY

1. FAUST, D. B., GILMORE, H. R., JR., and MUDGETT, C. S.: Chordomata: a review of literature, with report of a sacrococcygeal case, *Ann. Int. Med.*, 1944, xxi, 678-698.
2. BRUCE, J., and MEKIE, R.: Chordoma, *Surg., Gynec. and Obst.*, 1937, lv, 40-47.
3. MENDLOWITZ, M.: Clubbing and hypertrophic osteoarthropathy, *Medicine*, 1942, xxi, 269-306.
4. MARIE, P.: De l'ostéo-arthropathie hypertrophiante pneumique, *Rev. de méd.*, 1890, x, 1-36.
5. BAMBERGER, E. VON: Ueber Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten, *Ztschr. f. klin. Med.*, 1890, xviii, 193-217.
6. FRIED, B. M.: Chronic pulmonary osteoarthropathy. Dyspituitarism as probable cause, *Arch. Int. Med.*, 1943, lxxii, 565-580.

## A CASE OF A PUTRID EMPYEMA WITH A BRONCHO- PLEURAL FISTULA SUCCESSFULLY TREATED WITH PENICILLIN \*

By ARTHUR L. FORSGREN, M.D., *Minneapolis, Minnesota*

RAPID advances have been made in the treatment of empyema thoracis with the advent of penicillin, especially with its use intrapleurally. In all probability,

\* Received for publication March 24, 1947.

From Veterans Administration Hospital, Minneapolis, Minnesota, and the Department of Medicine, University of Minnesota.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

and a broncho-pleural fistula, the patient made a surprisingly prompt and uneventful recovery under intensive penicillin therapy. The patient received intramuscular penicillin, penicillin aerosol, and intrapleural instillations of penicillin.

The concomitant existence of a broncho-pleural fistula, in the cases of putrid empyemas successfully treated medically, demonstrates that such a fistula can

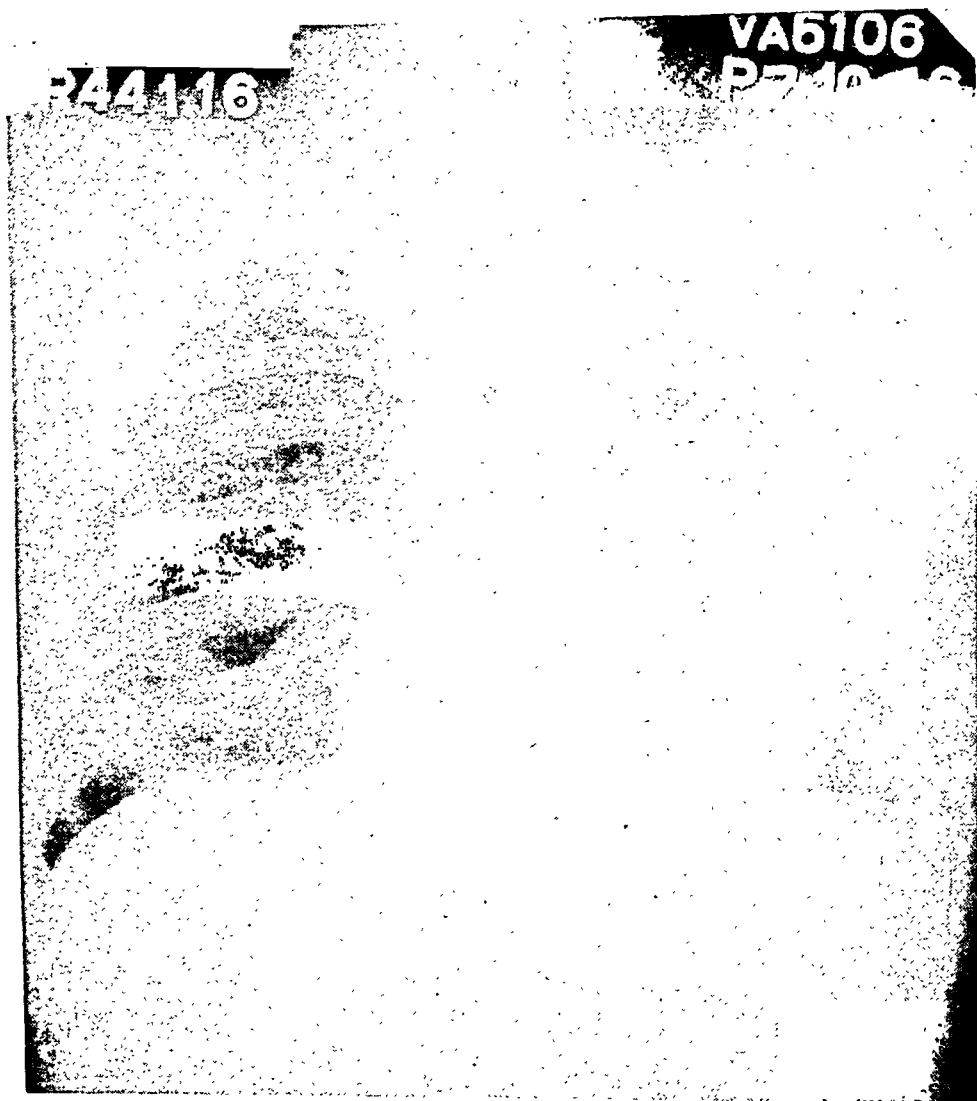


FIG. 2. During therapy.

heal without open drainage if the infection can be controlled. It also suggests that the fistula might have served a useful purpose in emptying the empyema cavity.

#### CASE REPORT

A 52 year old farmer first became ill during the last week of May, 1946. At this time he noted a sudden onset of chills and fever subsequent to the extraction of three abscessed teeth. The following day he had severe, anterior left chest pain on

were carious and moderately advanced pyorrhea was present. There was mucopurulent material in the pharynx. No cardiac abnormalities were noted; no organs or masses were palpable in the abdomen.

Examination of the chest revealed slight atrophy of the muscles over the left chest. The right lung was normal to auscultation and percussion. There was resonance over the left anterior lung, in the left axilla, and over the extreme upper portion of the left posterior lung. The lower three-fourths of the left posterior lung revealed dullness to flatness on percussion; tactile fremitus was decreased over this

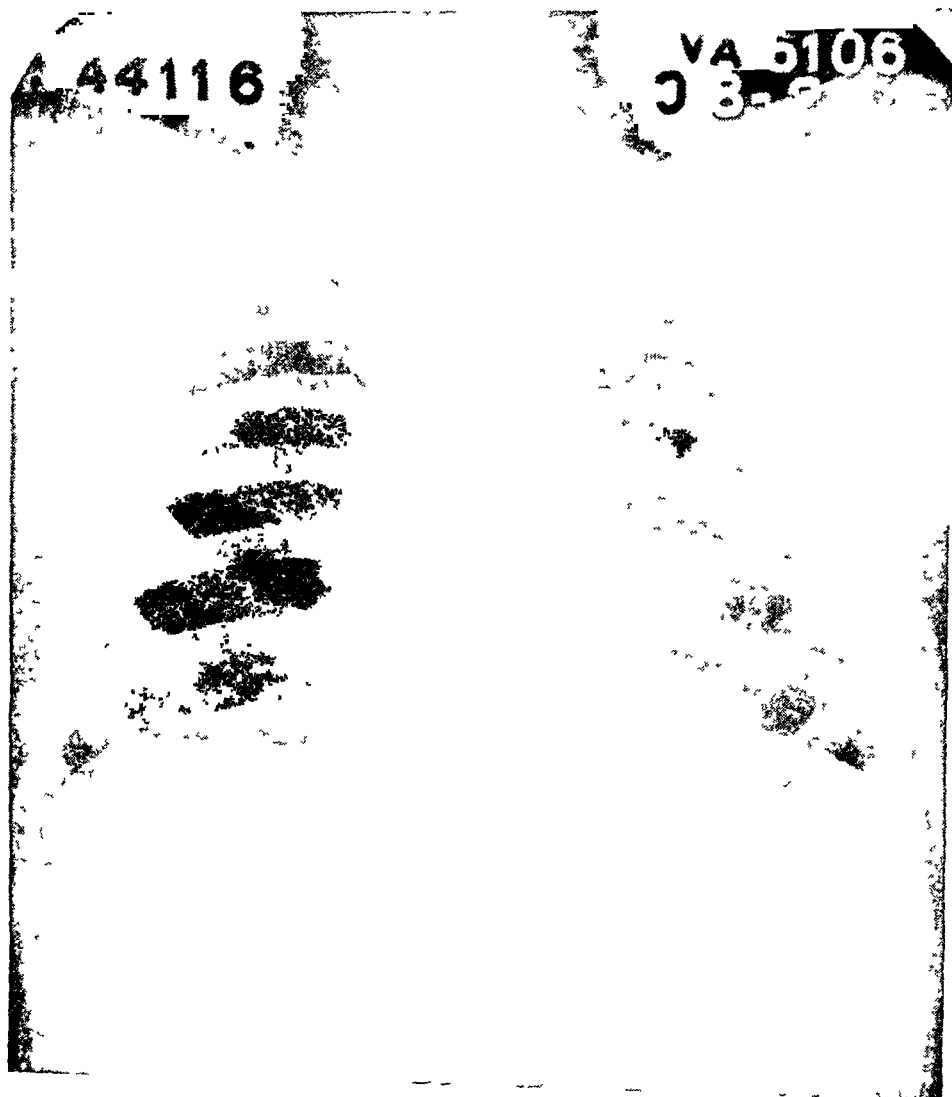


FIG. 4. After therapy.

area and the breath sounds were diminished though bronchial in quality. The sputum was green, purulent, and odorless.

Laboratory studies on admission showed the hemoglobin to be 11.8 gm., with 3,680,000 red blood cells. White count was 14,400, with 82 per cent neutrophiles, 15 per cent lymphocytes, and 3 per cent monocytes. Urinalysis showed a specific gravity of 1.015, with albumin and sugar negative. Postero-anterior chest roentgen-ray showed a density involving almost the entire left chest with an airfluid level in

After four penicillin instillations there was marked clinical improvement. Surgical intervention was not considered necessary. Chest roentgenograms showed marked diminution in the size of the cavity and in the amount of fluid. No fluid was obtained on thoracentesis. Intramuscular and nebulized penicillin was continued for two weeks, during which time the patient became asymptomatic and afebrile, the cough disappeared, and the white blood count fell to 7,500. The vital capacity increased to 2.9 liters. On August 1 all penicillin was discontinued. Chest roentgen-ray showed evidence of thickened pleura, as did physical examination, but no encapsulated fluid could be visualized. At this time the patient had gained 15 pounds since admission. The patient was discharged from the hospital on August 9, eight days after discontinuation of penicillin, no symptoms, febrile reaction, or positive physical findings having recurred.

The total period of hospitalization following diagnostic thoracentesis was four and one-half weeks.

Fifteen weeks after discharge from the hospital the patient was entirely asymptomatic and engaged in his normal farming activities:

### CONCLUSION

A case is presented demonstrating the cure of a putrid empyema with a broncho-pleural fistula obtained with penicillin therapy.

### BIBLIOGRAPHY

1. BROWN, BRUCE, ORY, EDWIN M., MEADS, MANSON, and FINLAND, MAXWELL: Penicillin treatment of empyema: report of 24 cases and review of the literature, *Ann. Int. Med.*, 1946, xxiv, 343-370.



organization of the pattern with loss of the regular sequences of rhythmic waves. The amplitude may be increased or diminished. There may be bilateral asymmetry, either in frequency or amplitude, of the waves. There may be "slow" waves (less than 8 per second), either isolated "random" waves, focal or diffusely scattered over the head; or such waves may come in regular sequences which are of great significance, especially if their amplitude is high. "Spikes" may occur, similarly distributed, brief, sharp-tipped waves, often of high amplitude.

Finally there is the well known "wave-and-spike" or "spike-and-dome" pattern, usually occurring in regular rhythmic series and generalized. This is always found during a clinical petit mal seizure, is often present in such cases in intervals between clinical seizures, and occurs occasionally between seizures in patients with convulsive attacks in whom no clinical petit mal seizures have been recognized. Although virtually pathognomonic of idiopathic epilepsy, this pattern has been reported as a sequel of encephalitis in children.

The first major application of the EEG to clinical diagnosis and perhaps the most important was in epilepsy, following the observations of Lennox and Gibbs. Immediately preceding a grand mal seizure highly characteristic changes occur, consisting often of numerous spikes associated with and eventually replaced by a generalized sequence of rhythmic slow waves of high amplitude. In the interval between seizures in some cases there are occasional short sequences ("bursts") of spikes, rhythmic slow waves, or both. Quite frequently there are only random scattered slow waves which are abnormal but not in themselves diagnostic, and in about 15 per cent of the cases no clear cut abnormality can be found.

The wave-and-spike pattern of the petit mal seizures has been noted. In "psychomotor epilepsy," episodes of abnormal behavior regarded by some as an "epileptic equivalent," Gibbs has described slow, notched or flat-topped waves, but others have questioned their significance as a manifestation of epilepsy.

Finally there is a group of clinically normal individuals, according to some constituting up to 15 per cent of the population, whose records show non-specific abnormalities, usually of minor degree.

Focal destructive lesions involving the cortex, including tumors, abscesses, local traumatic lesions, subdural hematomata and scars resulting from such lesions, cause definite abnormalities in many cases. The commonest manifestation of superficial cortical lesions is the occurrence of random slow waves, generally not equal or rhythmic, which are usually localized. More rarely there may be spikes alone or a mixture of spikes and slow waves, but only if the electrode is close to the tumor. There may be a similar disturbance in the symmetrical area on the other side but usually of lower amplitude. The abnormal waves do not arise from the tumor, which electrically is relatively "dead" tissue, but from the damaged cortex at the margin of the tumor. In the case of deep tumors the disturbance may be generalized.

As already noted, normal records are obtained in a significant percentage of patients with epilepsy or organic brain disease. Various procedures have been tried to elicit abnormalities in such cases, of which hyperventilation is the most useful and is now practically a routine procedure. Even in normal individuals, however, and particularly in children it tends to cause disorganization of the pattern and slowing of the activity, and care must be used in the interpretation. Injections of metrazol have been used, but the technic has not been adequately standardized.

Sleep or drowsiness causes marked changes in the EEG, depending upon the depth of sleep. The most important are a general slowing of the rate and the appearance of irregularly distributed slow waves of high amplitude which may be interpreted by the unwary as indications of disease. There is also a fast component, sequences of waves at 12 to 14 per second that often appear in the form of "spindles."

Records taken during sleep often yield information not obtained in waking records, particularly if they include shifts between the waking and sleeping state. Sleep may be natural or induced by hypnotics, of which seconal seems at present to be the most satisfactory. The characteristic changes in epilepsy may often be induced in this way; these are not masked by sleep, but they can be more easily recognized. Sleep markedly lessens the artefacts in the records due to gross muscular movement or tension, and it may be the only way of obtaining records in hyperkinetic or unruly children.

To be of value it is essential that the test be carried out with meticulous care by a thoroughly trained technician. The requirements in this respect are far more exacting than for any of the other diagnostic procedures in common use. Artefacts arising from technical errors or mechanical defects in the apparatus may simulate almost any of the pathological alterations that have been described. Particularly disturbing are spikes and waves of increased amplitude, either scattered or in sequence. Among the commoner sources of trouble are poorly applied or loosened electrodes, improperly placed electrodes, spread of electrode paste, sweating, swaying of the electrode wires, restless movements of the patient, blinking of the eyes, unrecognized drowsiness, faulty or "noisy" vacuum tubes and static electrical disturbances arising from sparking motors, diathermy or roentgen-ray machines. Tension or twitching of the cranial muscles, especially the temporals, causes "muscle spikes" which may obliterate other features of the tracing or, if sparse, may be mistaken for spikes of cortical origin.

The individual who interprets the record must be familiar with these artefacts and differentiate them from significant alterations. This is not always easy. He must be familiar with the standards of normal, which vary with age. In normal infants the records are poorly organized and show predominantly irregular slow activity. The shift to the adult pattern is gradual and is not usually attained until the fourteenth to eighteenth year. The record of any normal child is, therefore, likely to show aberrations from the adult pattern which would be pathological in an older age group.

## REVIEWS

*Clinical Allergy.* By LOUIS TUFT, M.D., Assistant Professor of Medicine, Temple University School of Medicine; Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital, Philadelphia, Pennsylvania. Second edition. 690 pages; 16 × 24 cm. Lea and Febiger, Philadelphia 6, Pennsylvania. 1949. Price, \$12.00.

In the opinion of this reviewer, Dr. Tuft's book is the best text on allergy available. The present volume is planned along lines similar to those followed in his original, or previous edition. However, it has been thoroughly rewritten and is modern in every sense. The volume is attractive in appearance, is a reasonable size, the type is clear, and the subject matter well arranged.

The author has retained his basic method of presentation in that the major divisions of the text are unchanged. First, general considerations of allergy are presented with a satisfactory discussion of the basic facts of anaphylaxis and allergy. This serves as an adequate orientation for the uninitiated and, in addition, will bring the practicing allergist abreast of current thinking about important phases of these subjects. The author then discusses etiological agents in groups, pointing out the important group characteristics of different types of allergens and calling attention to the clinical significance of these facts.

His discussion of the clinical manifestations of allergy, that is, the conditions one must treat practically, is sound, complete, and sufficiently free from confusing speculation to make it of great value in the clinical application of the vast amount of data his book contains.

In his discussion of the treatment of asthma, those of us who have used Butanefrine extensively will be disappointed to find no mention of this very valuable drug; particularly, when one considers the space given to other agents of doubtful value, some of which he condemns. This omission is difficult to understand.

This volume is a textbook in the best sense of the word. It is sufficiently dogmatic to permit the reader to chart a course clinically. Pertinent facts are given, doubtful data have been omitted. The author, also, avoids the temptation to coin new phrases and to add new classifications to the multiplicity of these now extant that dog the beginner in his attempt to see different phases of allergy clearly and with understanding.

Brief summaries of the different sections are again introduced with profit as are the comparative tabulations of differential diagnostic criteria in those conditions showing confusing similarities.

The section in which data are given on the place of occurrence of allergens and the technical procedures peculiar to allergy, is most valuable.

The newly included material on molds and antihistaminics is excellent and is presented with brevity and clarity as is usual with this author. However, the omission of the excellent bibliography included in the original edition represents a distinct loss, and it is unfortunate that the publishers deemed this necessary.

This book will be of great service to all physicians desiring to increase their knowledge of allergy. This should include all members of the profession.

H. M. B.

hardly correct to classify an agnosia among the cranial nerve lesions, even though it is qualified by the reference to the angular gyrus. Actually "optic agnosia" and "word blindness" are not synonymous. On page 7 one finds the statement, "circumferential blindness ('tubular vision') due to hysteria or retrobulbar neuritis." Retrobulbar neuritis notoriously causes a central scotoma and not a constriction of the peripheral fields. Under cranial nerve VIII the authors include, "sensory aphasia—(word deafness)," and "auditory hallucinations" as "symptoms of VIII nerve involvement." Similarly, "motor aphasia" is incorrectly listed among the "symptoms and signs of vagal involvement," as are "psychogenic disturbances." The latter are also included under the cranial nerves XI and XII. Psychogenic disturbances, aphasia, and agnosia involve disturbances of the cerebral cortex, and not of the cranial nerves.

Since this text has been planned to be concise, why the authors pay so much attention to the antiquated terminology commemorating the many pioneers in neurology is hard to understand. Many of the names listed are rarely used. Would it not be best to discourage their employment by omitting them, and using more meaningful designations, even if longer? For instance, under progressive muscular atrophies, among the bulbar types a "Fazio-Londe" syndrome is referred to. Wilson in his encyclopediac text merely refers to these two authors among many others who have described cases of subacute bulbar palsies. Also, why is it necessary to refer to the resistance to stretching the brachial plexus in neuritis of the latter, as Bielele's sign?

While the definitions of many terms are well done, the thumb-nail descriptions of the various disease entities and tumors are hardly sufficient for the beginner, and surely unnecessary for the initiate.

Perhaps the reader harbors a peculiar bias against compendia that make available skeletal material that can be exploited by those who are disinclined to make a more thorough study of neurology, no doubt "Correlative Neuroanatomy," barring its errors, has served many a medical student well in helping him prepare for examination.

H. A. T.

*Obstetric Analgesia and Anesthesia.* By FRANKLIN F. SNYDER. 401 pages; 16 × 24 cm. W. B. Saunders Company, Philadelphia. 1949. Price, \$6.50.

From the author's rich background of clinical and experimental investigation comes this interesting compilation of data concerning the various agents used in obstetrics to produce analgesia and anesthesia. The analysis of the physiologic and pharmacologic factors together with the survey of clinical case reports and conclusions, seemed to the reviewer to be particularly unbiased.

The work is divided into two sections, the first of which, comprising about half of the book, is a rather technical but clear exposition of fetal respiratory physiology and pathology, which proposes to prove that the fetal respiratory system is the site of greatest vulnerability to injury that proves fatal during labor or following it. It is also shown that intrauterine respiratory activity, like that seen after birth, takes place. Thus, breathing begins far back in embryonic life. It is indicated that since the functional significance of fetal respiration has been established, a new approach is open to the analysis of the hazards of labor to the child. The author describes much of his own fundamental experimental work on fetal respiratory physiology including assay of the pharmacologic factor in labor as illustrated by the action of various drugs in obstetric analgesia. He uses fetal respiratory movements as a sensitive indicator which can detect the earliest effect of narcosis. Results are expressed in terms of depression in activity of the fetal respiratory system and by impairment in the effective uterine expulsive mechanism. The first section is a background for the more clinical second section.

- Einführung in die Innere Medizin.* By DR. HANS JULIUS WOLF. 608 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$7.25.
- Das Ekg-ABC: Eine Systematik zur Auswertung von Elektrokardiogrammen.* By MAX WALDHECKER. 114 pages; 21 × 14.5 cm. (paper-bound). 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$2.25.
- Die Erkrankungen des Darmes. Anhang: Die Prokto-sigmoidoskopie.* By WALTER ZWEIG (London). 253 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$6.75.
- Grundlagen zur Erforschung des Alterns.* By DR. PAUL MATZDORFF. 248 pages; 23.5 × 15.5 cm. 1948. Verlag von Dr. Dietrich Steinkopff, Frankfurt/Main, Germany. Price, DM 13.50.
- Die Insulin-lipodystrophie.* By PROF. DR. FERDINAND ADALBERT KEHRER. 50 pages; 21 × 14.5 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$1.50.
- Die Konstitutionellen Vergrosserungen Umschriebener Körperabschnitte.* By PROF. DR. FERDINAND ADALBERT KEHRER. 293 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$8.50.
- Lehrbuch der Haut- und Geschlechtskrankheiten.* By DR. WALTHER SCHÖNFELD. 467 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$7.25.
- Lehrbuch der Klinischen Hämatologie.* By PROFESSOR DR. HANS SCHULTEN. 499 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$11.00.
- Leitfaden der Blutmorphologie.* By LYDIA SCHUDEL. 47 pages; 24.5 × 17 cm. (paper-bound). 1947. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$3.00.
- Die Lungentuberkulose.* By PROF. DR. MED. H. GISSEL and DR. MED. HABIL. P. G. SCHMIDT. 264 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$8.00.
- Marihuana in Latin America: The Threat It Constitutes.* By PABLO OSVALDO WOLFF, M.D., Ph.D., M.A., Buenos Aires, Argentina, Member of Expert Committee on Habit Forming Drugs of the World Health Organization. 56 pages; 20.5 × 13.5 cm. (paper-bound). 1949. Sponsored by Washington Institute of Medicine; published by The Linacre Press, Inc., Washington, D. C. Price, \$1.50.
- Medizinische Klinik ein Fortbildungskurs für Ärzte.* By PROF. DR. FERDINAND HOFF. 467 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$9.00.
- Modern Practice in Psychological Medicine—1949.* Edited by J. R. REES, M.D. 488 pages; 25 × 17 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$10.00.
- Neuere Tuberkuloseforschung I.* By OBERMEDIZINALRAT DR. GRIESBACH, Augsburg. 112 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$2.00.
- Outlines of Internal Medicine.* 6th Ed., First Printing. Edited by C. J. WATSON, M.D., Head, Department of Medicine, University of Minnesota. First four

# COLLEGE NEWS NOTES

## A.C.P. POSTGRADUATE COURSES

A schedule of the courses is repeated on the inside back cover page of this journal.

Although Course No. 1, **CARDIOLOGY**, at the National Institute of Cardiology of Mexico, had a registration of only twenty-five, due to the lateness of the announcement of the course, it was received with enthusiasm. Quoting from some of the reports received from those in attendance: "I spent a very profitable two weeks. The course was well-organized and well-conducted. I was very favorably impressed with the well-trained group of men there. The course gave me just what I wanted."—M.D., Tennessee. "In my opinion, it was the best course in Cardiology which it has been my privilege to attend. Its strong points were (1) the care with which the program was arranged; (2) the coördination between the Director and the heads of each department; and (3) the high level of instruction which each speaker maintained."—M.D., California. "A most profitable course and enjoyable vacation. The course is highly recommended, especially for catheterization technics and angiocardiology."—M.D., Texas. "The course was excellent beyond description. The courtesy of the staff and the zeal and interest of each participant has set a goal difficult to equal."—M.D., New York. "The program arranged by Dr. Chavez was informative and illuminating. Not only will the scientific program be forever remembered but likewise the hospitality of the Director. May I add that the enthusiasm and good fellowship displayed by Dr. George Morris Piersol, Dr. William Dock and Dr. George C. Griffith, American College of Physicians' guests, were deeply appreciated. I wish to express due thanks to The American College of Physicians for granting such opportunities to its members."—M.D., Pennsylvania.

When the course in Cardiology in Mexico is repeated, it is hoped that adequate notice of perhaps six or more months will be given to all members of the College, so that they can take advantage of this outstanding course.

Courses No. 2 and No. 3, **GASTRO-ENTEROLOGY** at the University of Chicago, and **CLINICAL NEUROLOGY** at Jefferson Medical College of Philadelphia, respectively, will have been concluded before the publication of this news item. In each case the registrations were reasonably large and representative. Reports from the men registered are not yet available, but from former experience it can be stated, with assurance, that no better courses in the respective fields could be arranged anywhere. Both courses have been given previously with signal success.

Those wishing to register for the remaining courses on the schedule should do so without further delay. Course No. 6, **THE BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO INTERNAL MEDICINE**, at the University of Wisconsin Medical School, is already registered to capacity and some of the other courses are approaching that point. Especially do Courses No. 7 and No. 8, **BLOOD DYSCRASIAS**, at the Medical College of Alabama, and **THE PHYSIOLOGICAL APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES**, at the University of Southern California School of Medicine, respectively, warrant increased registration, because there are still ample facilities available. Detailed outlines of all courses can be obtained from Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

---

## RESEARCH FELLOWSHIPS OF THE AMERICAN COLLEGE OF PHYSICIANS

Some months ago The American College of Physicians announced a limited number of Fellowships in Medicine and/or Pediatrics available from July 1, 1950

held at the Hotel New Yorker, New York City, November 14-18, 1949. The announcement states that the course is given with the coöperation of members of the staffs of the New York City medical schools and hospitals. Fee for the course is \$50.00. Information can be obtained from the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Ill.

---

#### POSTGRADUATE COURSE IN CARDIOLOGY AT DALLAS

A postgraduate course in Cardiology presented under the coöperation of the Dallas Academy of Internal Medicine, the Dallas Heart Association and the Faculty of Southwestern Medical School will be conducted at Dallas, November 28-December 1, 1949. The course will be held at the Melrose Hotel and Parkland Hospital. Applications for registration should be sent to the Dallas Southern Clinical Society, 433 Medical Arts Bldg., Dallas 1, Tex.

---

#### COURSE IN CLINICAL CYTOLOGY

McGill University and the Royal Victoria Hospital, Montreal, announce a two-weeks course in individual instruction in Cytological Technics and Interpretation, November 7-21, 1949, under the direction of Dr. J. Ernest Ayre. The tuition fee is \$100.00.

---

#### RESEARCH GRANTS AND FELLOWSHIPS TO BE MADE AVAILABLE IN 1950 BY THE LIFE INSURANCE MEDICAL RESEARCH FUND

Applications for 1950 grants in aid of research on cardiovascular problems will be received by the Life Insurance Medical Research Fund up to January 1, 1950. Support is available for physiological, biochemical, and pathological research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about \$550,000 will be awarded for these grants.

Applications for postgraduate fellowships for training in research in 1950-51 will also be received by this Fund up to January 1, 1950. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.) or the equivalent is required. The annual stipend varies, as a rule being between \$3,000 and \$4,000, with larger amounts in special cases. At least 12 postgraduate fellowships will be available.

New grants and fellowships will become available on July 1, 1950.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29, New York.

A number of pre-doctoral fellowships for basic training in research will also be awarded. Details are available on request.

---

#### FEDERAL GRANTS FOR NATIONWIDE ATTACK ON HEART DISEASE

The United States Public Health Service and the National Heart Institute recently announced grants of federal funds amounting to \$8,614,737 to 85 medical schools and research institutions in 34 states and the District of Columbia. Admin-

Dr. Roscoe L. Pullen, F.A.C.P., Seattle, Wash., has been appointed Professor of Graduate Medicine, Director of the Division of Graduate Medicine, and Vice-Dean of Tulane University of Louisiana School of Medicine, New Orleans, effective October 1, 1949.

---

Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, has succeeded Dr. Hugh J. Morgan, F.A.C.P., Nashville, as a member of the American Board of Internal Medicine.

---

Dr. William Walter Hargrave, (MC), USN, F.A.C.P., retired from active duty in the Navy on October 1, 1949, with the rank of Commodore. His last duty assignment was that as Senior Medical Officer and Head of the Department of Hygiene at the U. S. Naval Academy, Annapolis. Dr. Hargrave is now the Health Officer for the Campbell-Charlotte Health District, Rustburg, Va.



# ANNALS OF INTERNAL MEDICINE

---

VOLUME 31

NOVEMBER, 1949

NUMBER 5

---

## THE ETIOLOGY OF RHEUMATIC FEVER\*

By HOMER F. SWIFT, M.D., *New York, N. Y.*

ALTHOUGH a causative rôle of streptococcal infections with respect to rheumatic fever is fairly widely accepted, the evidence for this opinion seems insufficient for the hypercritical. There are at least three attitudes concerning this question: (1) Acceptance of the thesis and a readiness to apply it practically to public health aspects of the problem; (2) Relative indifference to the information that has been laboriously collected and correlated; (3) Skepticism and reiteration of the statement that the cause of this disease is unknown, or claims that an unidentified virus is the offending agent. It is imprudent to belittle the rôle of a devil's advocate in any philosophical, political, or scientific discussion, for when he performs his task wisely, he will prevent proponents of a thesis from falling into errors, which may have serious and even fatal repercussions in the medical disciplines. It is important, nevertheless, not to allow his arguments to overwhelm the significance of careful observations and thus prevent their effective utilization. In current propaganda and appeals to the public for funds to support research in this disease, it is wise not to have assertions of our ignorance belittle the importance of well established data. Because these data may not appear simple in their relationships, there is danger that they may be ignored and their practical significance be neglected. The purpose of this lecture is to assemble various elements in the puzzle of the rheumatic fever problem and to arrange them in a satisfactory design, with the qualification that the nature of science is to grow and rearrange the elements forming its structure.

Probably the discovery of the action of salicylates in alleviating the toxic and painful manifestations of rheumatic fever materially hindered fundamental investigation of this disease. The symptomatic relief induced created a false sense of accomplishment; and not until several decades after

---

\* Kober Lecture, delivered at Georgetown University Medical Center, Washington, D. C., March 28, 1949.

Delivered in part before the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., April 1, 1949.

From the Hospital of The Rockefeller Institute for Medical Research, New York City.

A forward step in streptococcal classification resulted from Schottmüller's blood agar plate technic for distinguishing hemolytic from nonhemolytic streptococci,<sup>3</sup> and the demonstration that the former comprised the more virulent strains. The frequent association of subacute bacterial endocarditis (endocarditis lenta) with chronic rheumatic valvular disease led many physicians to conclude that both conditions had as common causative agents the nonhemolytic streptococci which induced the finally fatal infection. This opinion was supported by the occasional post mortem recovery of viridans streptococci from the heart's blood of rheumatic subjects, for formerly bacteriologists little appreciated how rapidly, during the death agony or post mortem, green streptococci or enterococci may invade the blood stream from the mouth or intestines where they normally reside. Moreover, the temporary entrance into the blood of lowly virulent nonhemolytic streptococci following nose and throat operations, tooth extractions, instrumentation of the urethra or ureters, or manipulation of intensely inflamed pharyngeal tissues are phenomena, discovered in the past three decades, that explain the occasional recovery of green streptococci from the blood of rheumatic patients during life. It is, indeed, readily understandable how rheumatic fever-inducing properties were attributed to lowly virulent nonhemolytic streptococci, because the lesions they induce are usually nonpurulent, a characteristic of those of rheumatic fever; while in contrast, hemolytic streptococci are often pyogenic. Indeed, the impossibility of demonstrating pyogenic streptococci either in cultures of rheumatic exudates or proliferates, or microscopically in the visceral, articular, or subcutaneous lesions of rheumatic fever patient are features that could blind investigators to their potential pathogenic rôle in this disease. It appeared probable, moreover, that if the rheumatic lesions were invaded by streptococci, such lesions would more readily dispose of the easily phagocytatable viridans varieties than of the more virulent pyogenic hemolytic strains. Indeed we formerly attributed to the viridans streptococci a possible etiologic rôle in rheumatic fever, an opinion that now seems incorrect; but it stimulated animal experimentation and the study of the host-parasite relationships which eventually seem to have added to knowledge concerning this disease. Before discussing these experiments, it is advisable to orient ourselves concerning modern streptococcal bacteriology.

In the early 1920's the classification of streptococci was based mainly upon three general procedures: (1) determining their action on blood; (2) testing their ability to attack certain chemical substances of known composition which were added to artificial culture media; and (3) ascertaining their capacity to survive under critical chemical and thermal environments.<sup>4</sup> While identification on such biochemical bases is sometimes definitive, notably with *Streptococcus mastitidis*, *Streptococcus equi*, the enterococci and *Streptococcus lactis*, many other streptococci have several common biochemical capacities but different pathogenic potentialities; hence the resulting

## SOMATIC ANTIGENIC COMPONENTS

Groups are recognizable serologically because the strains within a group elaborate in common a group specific carbohydrate called C which gives a precipitin reaction in vitro when combined with its group specific antibody. Many groups are further divisible into serological types. The type specific components are sometimes polysaccharides, for example in group B, and sometimes, notably in group A, they are proteins which are designated type specific M substances.

The typing of group A streptococci stems primarily from the ability of a particular strain to induce in animals the ability to resist infection with that strain and also with other strains that elaborate a homologous type specific M protein. This resistance or type specific immunity may be actively induced by nonlethal infections, and also by parenteral injections of vaccines prepared from strains elaborating type specific M protein, but not from strains lacking this capacity. The serum of actively immunized animals

TABLE II  
Somatic Antigens of Group A Streptococci

Somatic Antigens	Antibodies	Specificity
C carbohydrate	Anti C precipitins	Group specific
Nucleoproteins	Antinucleoproteins	Common to many cocci
proteins	Anti T agglutinins	Some type specific; some common to several types
M proteins . . . . .	Protective	Type specific
	Bacteriostatic	in vivo
	Anti M precipitins	in vitro
	Anti M agglutinins	in vitro*

\* With properly absorbed sera.

when injected in sufficient quantities into other animals protects them from infections with streptococci belonging to homologous types, but not from heterologous types.

Sera having this type specific protective capacity contain type specific antibodies. Of these, the most easily recognizable in vitro are anti M precipitins, which form precipitates after mixing suitable extracts of the streptococci in question with properly absorbed sera from highly immunized rabbits. Sera of men or animals infected with group A streptococci, or immunized with these bacteria, also contain agglutinins which may have type specific significance, provided accompanying non-type-specific agglutinins are suitably absorbed from the sera. This important proviso requires attention because many group A streptococci contain another somatic agglutinin, called T, that sometimes bears a close type relationship to an accompanying M protein, and at other times does not. For example, types 4, 24, 26, 28, 30 and 44 elaborate T antigens so closely related that on the basis of agglutination tests with unabsorbed sera no single one of these types

extracts containing only M protein, for they usually contain residual antigenic substances that yield cross reactions with unabsorbed sera. In fact, suitable extracts prepared from group A hemolytic or viridans streptococci, pneumococci, or even staphylococci contain nucleoproteins which give cross complement fixation reactions with the sera of animals immunized with several varieties of streptococci, and with sera of patients suffering from subacute viridans streptococcal endocarditis, from acute group A streptococcal respiratory infections, or from pneumococcal pneumonia.<sup>9</sup> These results indicate that, in addition to the group or type specific components, the several members of the coccus family form somatic antigenic mosaics containing nucleoprotein-like substances with similar chemical configuration. Such phenomena point to the need for caution in interpreting the significance of both in vivo and in vitro tests performed with only partially purified streptococcal extracts.

### EXTRACELLULAR ANTIGENIC COMPONENTS

The serological reactions just discussed involve somatic antigens contained in streptococcal cells. Human subjects and animals while undergoing group A streptococcal infections or artificial immunizations, often form antibodies against extracellular products of streptococci. These extracellular antigens are elaborated into media nurturing these microorganisms and into the tissues of animals harboring them. Among the many extra-

TABLE III  
Extracellular Antigens of Group A Streptococci

Extracellular Antigens	Antibodies	Relative Antibody† Production in Human Infections	
		No RF	RF
Streptolysin O	Antistreptolysin O	++	+++
Streptolysin S	Antistreptolysin S	++	+
Streptokinase (Fibrinolysin)	Antistreptokinase	++	+++
Hyaluronidase (Types 4 and 24) (Hyaluronidase precursor?)* all types	Antihyaluronidase	++±	++++
Proteinase	Antiproteinase	(+)?	(+±)?
Desoxyribonuclease (Dornase)†	Anti-DORNase†	+	++
Ribonuclease	Antiribonuclease	?	?
Erythrogenic toxin	Antitoxin	?	?

\* The existence of a precursor is assumed because of the frequent stimulation of streptococcal antihyaluronidase following most group A streptococcal infections.

† The abbreviation DORN is derived from DesOxyRiboseNuclease (Tillett et al.).

‡ The designation "relative" refers to statistical analysis of groups of patients and not to one individual.

cellular antigens, those longest studied are erythrogenic toxins, streptolysin O, and fibrinolysin, more accurately designated streptokinase; others have more recently attracted attention.

It is now generally accepted that scarlet fever is caused by group A streptococci that elaborate a rash-inducing toxin against which the patient possesses no effective antitoxic immunity when infected. This toxin cir-

tritional environment by group A streptococci and their respective antibodies require consideration.

Hyaluronic acid, hyaluronidase and antihyaluronidase have recently attracted considerable attention with respect to a possible pathogenic relationship in rheumatic fever. This acid, a highly viscid polysaccharide, makes up the capsules formed by many streptococci belonging to groups A and C.<sup>15</sup> Its presence bears close relationship to the virulence of "animal" group C streptococci,<sup>16</sup> but it has only slight significance in the virulence of group A strains.<sup>17, 18</sup> Hyaluronic acid is widespread in the bodies of vertebrates, notably in the umbilical cord, vitreous humor, synovial fluid, and in the interfibrillar cement substance of collagen.<sup>15</sup> Enzymes that split it are designated hyaluronidases, and several have been described from different sources: leech heads, mammalian testicular extracts, groups A and C streptococci, pneumococci, staphylococci and clostridia. While the common action of the enzymes from these different sources is to split any hyaluronic acid into less complex and viscid products, each hyaluronidase appears to be antigenically specific according to its respective origin; e.g., antihyaluronidase in the serum of persons infected with group A streptococci does not react with hyaluronidase from other bacteria. Three technics for demonstrating hyaluronidase have been employed: mucin clot solution; turbidity reduction; and as a spreading factor (Duran-Reynals<sup>19</sup>). Antibodies against hyaluronidases are measured by their ability to prevent these actions. With the mucin clot prevention technic and a substrate from umbilical cords, hyaluronidase production has been demonstrable only with type 4 and type 22 group A streptococci<sup>20</sup>; but Pike,<sup>21, 22</sup> employing the turbidity reduction technic with hyaluronic acid from streptococcal capsules, found hyaluronidase production by over half of his noncapsulated group A strains and even by some capsulated strains. The possibility that most group A strains form this enzyme, usually as a precursor must be entertained, for although it is difficult of demonstration *in vitro*, the fact that most patients infected with group A streptococci elaborate streptococcal antihyaluronidase indicates its widespread occurrence in these microorganisms. The degree of this antibody response, moreover, suggests that hyaluronidase is a very strong antigen, possibly the strongest of the extracellular antigens.

New born babies have practically the same streptococcal antihyaluronidase content in their sera as is present in that of their mothers; but this disappears within six months. Beginning in the three to five year age period, this antibody begins to appear with a slowly increasing frequency, until the age group of 20 years. The relative frequency curve then remains constant until the 60 year age group, when it falls slightly.<sup>23, 24</sup> This phenomenon, and the demonstration of antibodies against erythrogenic toxin slowly increasing with age, reflect roughly the occurrence of group A streptococcal infections in a considerable portion of the population.

Carefully gathered data moreover have demonstrated that the precursory streptococcal infection may be so mild as to escape clinical detection. For example, Kuttner and Krumwiede<sup>35</sup> showed that during epidemics in a closed institution, streptococci appeared for a few days in the nasopharynges of some children, who then sometimes had slight leukocytosis, and subsequently developed in their sera increasing titers of antistreptolysin O. Others have confirmed this observation under epidemic conditions. Thus was explained the old observation that rheumatic fever occurs at times without an obvious nasopharyngitis as a forerunner: it may be too mild for accurate clinical detection.

#### REACTIONS IN PATIENTS' SERA WITH EXTRACELLULAR STREPTOCOCCAL ANTIGENS

The streptococci inducing the precursory infection, moreover, disappear from the nose and throat before the onset of the rheumatism in a quarter to a third of the patients; hence other evidence of the precursory streptococcal activity is requisite; and the need has been supplied mostly by study of antibodies against the extracellular antigens of group A streptococci. Among these the antistreptolysin O test, devised by Todd,<sup>10</sup> has been most extensively employed; and with it between 80 and 90 per cent of rheumatic fever patients have been shown to develop abnormal amounts of antistreptolysin O in their sera. This is also true of most patients infected with group A streptococci; hence, this reaction is not diagnostic of rheumatic fever, but of group A streptococcal infections. That such infections may occur without inducing antistreptolysin O formation has already been noted; hence this test has only relative, not absolute value.

The application of technic for detecting antifibrinolysin,<sup>12</sup> and more recently for titering antistreptokinase quantitatively,<sup>14</sup> has still further confirmed the nature of the precursory respiratory infection, for sometimes there is an increase in antistreptokinase but no rise in antistreptolysin O, and vice versa. Several observers have reported a relatively higher content of these two antibodies in rheumatic than in non-rheumatic subjects, without having information concerning the antigenic composition of the streptococci infecting their patients; hence it was not known definitely whether the relatively greater antibody formation by the rheumatic group was due to differences in the parasites' activities or in the hosts' responses.

This question is apparently answered by the observations of Anderson, Kunkel, and McCarty<sup>36</sup> in a study of an epidemic in patients infected with strains of one or more of three different types of group A streptococci; so the antigenic stimulus was probably similar. Although, as in all such studies, there was marked variation among individuals, the group which had rheumatic sequelae developed distinctly more antistreptolysin O and antistreptokinase than did those who remained free of rheumatism. Other noteworthy observations were recorded: (1) those patients effectively treated

trary to experience: although it has been demonstrated that among group A streptococci only types 4 and 22 produce hyaluronidase in amounts sufficient to be easily detected in vitro, nevertheless, in at least two epidemics caused by type 4 streptococci in rheumatic subjects, no rheumatic recurrences were induced, while rheumatic fever frequently follows infections with streptococci that produce relatively little hyaluronidase. Furthermore, group C streptococci, quite frequent producers of considerable amounts of hyaluronidase, have likewise not been observed to induce rheumatic fever; and pneumococci, staphylococci and clostridia, also potent producers of this enzyme, are conspicuously negative as inducers of rheumatic fever.

The report by Guerra<sup>40</sup> that hyaluronidase (probably in testicular extracts) acted as a spreading agent (Duran-Reynals<sup>39</sup>) more powerfully in rheumatic fever subjects than in non-rheumatics, and that this spreading action is inhibited in guinea pigs by salicylates, has also excited renewed interest in the possible hyaluronidase-antihyaluronidase question with respect to rheumatic fever. Harris and Friedman<sup>41</sup> employing relatively weaker concentrations of streptococcal hyaluronidase were unable to demonstrate any unusual susceptibility to this spreading factor in rheumatic fever subjects compared with non-rheumatics. They suggest that the differences in their results from Guerra's were due to the strong irritating effects of the extracts used by the latter, and that these nonspecific effects might easily lead to misinterpretation of the results he observed.

Until more light is thrown on the whole hyaluronidase subject, it seems well to assume that the relatively more marked antihyaluronidase formation by rheumatic fever patients, compared with that of patients with simple streptococcal infections, is a concomitant rather than a causal phenomenon with respect to rheumatic fever.

The question of antistreptolysin S production by rheumatic fever patients has received relatively little attention, probably because of technical difficulties in producing this antigen for in vitro studies. Todd, Coburn and Hill<sup>42</sup> reported that antistreptolysin S was more abundant in the sera of patients suffering from simple group A streptococcal infections than in that of patients with rheumatic sequelae, even though the latter contained more than was found in normal persons' sera. With better methods for preparing streptolysin S, reported by Bernheimer,<sup>29</sup> investigations of the relationship of this lysin to various manifestations of streptococcal infections will probably be resumed.

The occurrence in a patient's serum of antibodies against the extracellular components of group A streptococci merely indicates a previous infection with some strain belonging to this group, but has no significance with respect to any particular strain or type. Furthermore, the finding of abnormal concentrations in a single serum is not definitely indicative of a recent streptococcal infection, because fairly high titers of antistreptolysin O, anti-streptokinase, or streptococcal antihyaluronidase may persist in a patient's serum for many months, possibly years, after a streptococcal infection. If

tions, and the quantitative antistreptokinase test was not yet available; but a study of the comparative development of the other three antibodies was possible. The rheumatic fever group developed relatively average higher antibodies than did the non-rheumatic group when tested with these four different technics. Although the average measurable antibodies against the extracellular antigens appeared at practically the same time following infection in all groups of patients, there was an average delay of approximately two to three weeks in the appearance of antibodies against the somatic antigens among the rheumatic fever group as compared with the non-rheumatic; this is illustrated in the bacteriostatic and anti M precipitin tests, and confirms earlier less extensive studies.<sup>44, 45</sup> The possible significance of this delay in the pathogenesis of rheumatic fever is not as yet evident.

Chart 2, summarizing graphically the antibody production by a comparable series of our patients indicates that the more tests that are applied to the same lot of sera, the more convincing is the evidence of a previous recent

Distribution of 4 different antibodies  
in 83 patients infected with Group A streptococci

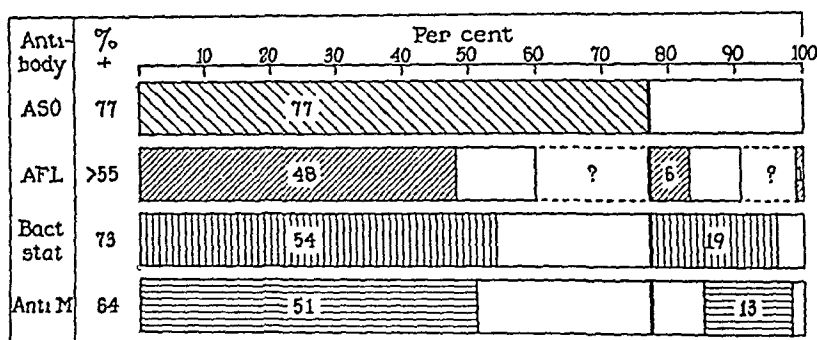


CHART 2.

streptococcal infection. Among patients undergoing 83 different group A infections, whose sera were repeatedly tested for antistreptolysin O, antifibrinolysin, bacteriostatic and anti M precipitin reactions, it was found that the first appeared in practically three-fourths of the cases; but among the patients' sera containing no antistreptolysin O, there was nevertheless a demonstrable formation of antifibrinolysin, bacteriostatic antibodies, or anti M precipitins; hence application of four tests indicates there was antibody formation against one or more streptococcal antigenic components in all instances.

A detailed analysis of this entire series of patients in whom it was possible to initiate the investigations very near the time of onset of their streptococcal infections and to continue them through the period when rheumatic sequelae were apt to occur, and in the event of the appearance of these sequelae for several months and sometimes for two or three years, showed the following: at the onset of an infection with a given type of group A streptococci, a patient's serum contained no bacteriostatic antibodies against that type, al-



demonstration that in one person suffering from repeated respiratory streptococcal infections, each attack has been induced by a group A streptococcus different in type from those shown to have caused previous attacks. This leads directly to the concept that in many people suffering from successive streptococcal infections, each infection is probably induced by group A streptococci different in type from those that caused prior infections in that person.

The varieties of nosologically definable diseases induced in human beings by group A streptococci are probably more numerous than is the case with any other microorganism. None of them, e.g., erysipelas or scarlet fever, is caused exclusively by a single serological type of streptococcus. The characteristic rash of scarlet fever is a peculiar response to an erythrogenic toxin elaborated by strains belonging to several types. Surgical or obstetrical streptococcal infections owe their peculiarity in part to the body areas invaded by the microorganisms, and in part to their virulence. In a streptococcal epidemic due to a single strain, such as occurs in milk-borne infections, and in families, institutions and barracks, many different clinical manifestations are observed; and this suggests that variations in the tissues of different persons are factors which help to condition the clinical pictures.

Powers and Boisvert<sup>49</sup> have outlined the changing types of response to streptococcal infections of the respiratory tract encountered at various age periods. In the very young, the symptoms are least clear cut; the nasopharyngitis is diffuse, of several weeks' duration, and prone to spread to the accessory sinuses and middle ears. The picture may be so noncharacteristic that its etiology can only be determined bacteriologically. Not uncommon is eczematoid dermatitis or vaginitis due to the same streptococci that are inducing upper respiratory infection. In school children, the nasopharyngeal response is somewhat more circumscribed and intense, the general symptomatology more stormy, the duration of a single infection shorter than in the very young. At the end of the first and in the second decade, especially after puberty, the course is usually still more acute, the fever higher, the duration shorter, the nasopharyngeal response more focalized and intense. Such turbulent and relatively brief acute courses exemplified by an attack of tonsillitis, are common in the third and fourth decades of life; and after 40, streptococcal respiratory infections are relatively much rarer than in the earlier age periods, which suggests that with advancing age a fairly effective immunity has developed.

Because these trends of streptococcal diseases towards localization resemble comparable phenomena seen in tuberculosis, Powers has designated the whole group of streptococcal diseases, "streptococcosis." It seems to me that because of the multiplicity of their clinical manifestations they may be more usefully compared with those of syphilis. This disease is currently so modified by antibiotics and other drugs that its normal evolution is difficult to observe.

In untreated or poorly treated syphilitic patients, the first response at the site of inoculation is a hard chancre, which is followed within a few weeks by

this has been one of the objectives of experiments in our laboratories; and while there were many failures in attaining the primary objective, still much information was obtained which, with simultaneous studies of streptococcal infections in rheumatic patients, has apparently advanced our conception as to how streptococci may act to induce this disease. The pertinent data deriving from those investigations follow.

The earlier researches were carried out with rabbits infected intracutaneously with viridans streptococci. By employing suitable strains, it was shown that after the primary inflammatory response had subsided there often appeared, at the sites of the original inoculations, secondary reactions lasting for one to five days.<sup>50</sup> These reactions resembled somewhat those described by Koch in guinea pigs infected with tubercle bacilli, and in many respects differed from the Arthus phenomenon in rabbits injected with foreign serum.<sup>51</sup> This state of bacterial hyperreactivity could be distinctly increased and prolonged by repeated minute focal inocula of the streptococci. Indeed, it seemed to derive, to a considerable degree, from inflammatory foci, for when comparable doses of the same lowly virulent streptococci were injected intravenously into rabbits the focal responses to subsequent intracutaneous inoculation were less marked than in normal controls; in other words a state of immune hyporeactivity had been induced. It was next shown that by injecting lowly virulent strains of hemolytic streptococci, or heat-killed cultures, the state of hyperreactivity was induced by intracutaneous inoculation and a state of immune hyporeactivity by intravenous injections.<sup>52</sup> It was then found that although rabbits immunized intravenously with a strain of viridans streptococci developed a state of immune hyporeactivity to intracutaneous challenge with that strain, their response to a simultaneous challenge with a group A or a group C strain was that of hyperreactivity.<sup>53, 54</sup> Also noteworthy was the observation that two or three months after stopping the intravenous immunization, there developed a state of hyperreactivity to challenge with the immunizing strain.<sup>54</sup> Subsequently, when the significance of successive human infections with several different serological types of group A streptococci was appreciated, it was shown that prolonged intravenous immunization of rabbits with one type of group A streptococci or repeated intracutaneous infections with one fairly virulent type, usually induced the animals' tissues to respond subsequently to suitably sized intracutaneous inocula as follows: immune hyporeactivity to challenge with homologous type strains; and frequently, though not always, the same animals showed cutaneous hyperreactivity to inoculation with heterologous type strains.<sup>55</sup>

#### RHEUMATIC FEVER-LIKE CARDITIS FOLLOWING SUCCESSIVE INFECTIONS WITH DIFFERENT TYPES OF GROUP A STREPTOCOCCI

The probable import of one person having several streptococcal upper respiratory tract infections each with a different type of group A streptococci was at that time becoming increasingly insistent, for it seemed that with each

the adrenal cortex and the occurrence of myocardial granulomata in the rabbits dying, or sacrificed while sick, following the last of several cutaneous streptococcal infections. Several different sets of controls indicate that the experimental conditions apparently conducive to the induction of the lesions described were successive focal lesions caused by group A streptococci of different serological types.

From the results of these experiments it would seem unwise to assume, unreservedly, that rheumatic fever had been induced in these rabbits; but, on the other hand, to deny this possibility, in view of the data presented, would also be unjustified. Those investigators, notably Klinge and his collaborators<sup>57</sup> and Rich and his coworkers,<sup>58</sup> who have emphasized many points of similarity between the carditis seen in rabbits receiving one or more injections of foreign protein and that of rheumatic fever, have argued that these histopathological analogies indicate an "allergic factor" as being common to the two pathological states. It has been emphasized by Ehrlich et al.,<sup>59</sup> however, that there are enough histological diversities in the two conditions to indicate that they are not strictly comparable. Many years ago, in discussing Klinge's investigations, Aschoff<sup>60</sup> emphasized the hazard of attempting to establish the causation or essential nature of a disease by comparing one or two points of analogy with those of another disease. He insisted, that to prove a common causative factor in two such comparable conditions, a single common stimulus must be employed.

In investigating a possible etiological rôle of suspected microorganisms in a given disease and in planning a working hypothesis to test whether, and how, these microorganisms may induce this disease experimentally, it would seem quite important to duplicate, as closely as possible, the particular chain of circumstances under which these agents appear to induce the typical disease in nature. In the earlier part of this lecture are outlined the data obtained from applying current knowledge of group A streptococci and their antigenic components to the bacteriological and immunological studies of rheumatic fever patients; in the latter part is summarized how these data have been utilized in studying experimental streptococcal infections in rabbits. Eventually, by imposing on these animals infectious conditions approximately similar to those observed among rheumatic fever patients, there has been induced a histopathological picture in their hearts closely resembling that of human rheumatic carditis. The small proportion of infected rabbits showing this picture roughly approximated the relative frequency of rheumatic fever encountered among patients infected with group A streptococci.

On the basis of these investigations and of the hypothesis employed in planning them, there seems to be furnished additional support to the theory that group A streptococci are important factors in the pathogenesis of rheumatic fever; and the investigations also indicate how these microorganisms may act in giving rise to this disease.

25. ELLIOTT, S. D.: A proteolytic enzyme produced by group A streptococci with special reference to its effect on the type-specific M antigen, *Jr. Exper. Med.*, 1945, lxxxi, 573.
26. McCARTY, M.: The occurrence of nucleases in culture filtrates of group A hemolytic streptococci, *Jr. Exper. Med.*, 1948, lxxxviii, 181.  
Personal communication about antibody formation by patients.
27. WATSON, R. F.: Personal communication.
28. HERBERT, D., and TODD, E. W.: The oxygen-stable haemolysin of group A haemolytic streptococci (streptolysin S), *Brit. Jr. Exper. Path.*, 1944, xxv, 242.
29. BERNHEIMER, A. W., and ROBBART, M.: The effect of nucleic acids and of carbohydrates on the formation of streptolysin, *Jr. Exper. Med.*, 1948, lxxxviii, 149.
30. COBURN, A. H.: The factor of infection in the rheumatic state, 1931, Williams and Wilkins Co., Baltimore.
31. SHELDON, W.: On acute rheumatism following tonsillitis, *Lancet*, 1931, i, 1337.
32. SCHLESINGER, B.: The relationship of throat infection to acute rheumatism in childhood, *Arch. Dis. Child.*, 1930, v, 411.
33. GRIFFITH, F.: Types of haemolytic streptococci in relation to scarlet fever, *Jr. Hyg.*, 1926, xxv, 385.
34. GLOVER, J. A., and GRIFFITH, F.: Acute tonsillitis and some of its sequels; epidemiological and bacteriological observations, *Brit. Med. Jr.*, 1931, ii, 521.
35. KUTTNER, A. G., and KRUMWIEDE, E.: Observations on the effect of streptococcal upper respiratory infections on rheumatic children—a three-year-old study, *Jr. Clin. Invest.*, 1941, xx, 273.
36. ANDERSON, H. C., KUNKEL, H. G., and McCARTY, M.: Quantitative antistreptokinase studies in patients infected with group A hemolytic streptococci: a comparison with serum antistreptolysin and gamma globulin levels with special reference to the occurrence of rheumatic fever, *Jr. Clin. Invest.*, 1948, xxvii, 425.
37. FRIOU, G. J., and WENNER, H. A.: On the occurrence in human serum of an inhibitory substance to hyaluronidase produced by a strain of hemolytic streptococcus, *Jr. Infect. Dis.*, 1947, lxxx, 185.
38. QUINN, R. W.: Antihyaluronidase studies of sera from patients with rheumatic fever, streptococcal infections, and miscellaneous non-streptococcal diseases, *Jr. Clin. Invest.*, 1948, xxvii, 471.
39. HARRIS, T. N., HARRIS, S., and NAGLE, R. L.: Studies in the relation of the hemolytic streptococcus to rheumatic fever. VI. Comparison of streptococcal antihyaluronidase with antibodies to other streptococcal antigens in the serum of patients with rheumatic fever and acute streptococcal infection: mucin clot prevention test, *Pediatrics*, 1949, iii, 482.
40. GUERRA, F.: Hyaluronidase inhibition by sodium salicylate in rheumatic fever, *Science*, 1946, ciii, 686.
41. HARRIS, T. N., and FRIEDMAN, S.: Studies in the relation of hemolytic streptococci to rheumatic fever. IV. Effect of streptococcal spreading factor in rheumatic patients and others, *Am. Jr. Dis. Child.*, 1949, lxxvii, 561.
42. TODD, E. W., COBURN, A. F., and HILL, A. B.: Antistreptolysin S titres in rheumatic fever, *Lancet*, 1939, ii, 1213.
43. ROTHBARD, S., WATSON, R. F., SWIFT, H. F., and WILSON, A. T.: Bacteriologic and immunologic studies on patients with hemolytic streptococcal infections as related to rheumatic fever, *Arch. Int. Med.*, 1948, lxxxii, 229.
44. SWIFT, H. F., and HODGE, B. E.: Type-specific anti-M precipitins in rheumatic and non-rheumatic patients with hemolytic streptococcal infections, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 849.
45. COBURN, A. F.: Observations on the mechanism of rheumatic fever, *Lancet*, 1936, ii, 1025.
46. WATSON, R. F., ROTHBARD, S., and SWIFT, H. F.: Type-specific protection and immunity following intranasal inoculation of monkeys with group A hemolytic streptococci, *Jr. Exper. Med.*, 1946, lxxxiv, 127.

# SODIUM SUCCINATE—AN ANALEPTIC FOR BARBITURATE POISONING IN MAN \*

By RICHARD H. BARRETT, M.D., M.Sc., *Hanover, New Hampshire*

THE barbiturates, next to carbon monoxide, are the most frequent source of poisoning, both suicidal and accidental.<sup>2</sup> This may well be attributable to the widespread use of the barbiturate drugs<sup>1</sup> as evidenced by the fact that in 1945, alone, over 290 tons of this one group of hypnotics were produced.

This paper reports an investigation of the effects of a new analeptic agent, sodium succinate, in the treatment of poisoning with barbituric acid compounds.

The present and generally accepted treatment of barbiturate poisoning<sup>3</sup> consists of one or all of the following procedures with, possibly, others: (a) Administration of oxygen, alone or in combination with carbon dioxide, to combat anoxia; (b) administration of intravenous fluids, to increase, supposedly, kidney filtration and thereby remove the barbiturate, at an increased rate; (c) gastric lavage, employed very early, in an attempt to remove the depressant drug, provided it were ingested; and (d) probably the most outstanding of all, the use of various convulsant drugs given intravenously. Picrotoxin, an outstanding example of the convulsants, first came into general usage in 1936. Since that time, it has been the drug most commonly used in the treatment of barbiturate poisoning.<sup>4</sup>

One may accept readily the use of oxygen and certain intravenous fluids as supportive therapy. However, gastric lavage should be used rarely, if ever, on a comatose patient with suspected barbiturate poisoning, because of the danger of inducing vomiting and consequent aspiration of stomach contents.

The use of convulsant drugs in the treatment of barbiturate poisoning while justified in critical situations is not without danger. In accidental and, especially, in suicidal barbiturate poisoning, exact dosage and type of barbiturate consumed is rarely known; therefore, a safe dosage of convulsant is difficult to determine. It has been stated that should a convulsion develop during the use of a convulsant drug, the convulsion may be controlled easily by giving more barbiturate.<sup>4</sup> This procedure could lead to disastrous results. Certain convulsants, given in subconvulsant doses, may prolong the later stages of recovery from the effects of hypnotics, and this secondary depression may be accompanied by pulmonary edema.<sup>5</sup> Hence there is possibility of underdosage, as well as overdosage.

\* Presented at New England Sectional Meeting of the American College of Physicians, January 28, 1947.

From the Hitchcock Clinic, Mary Hitchcock Memorial Hospital, Hanover, New Hampshire.

sibility of a reflex mechanism, based on the hypertonicity of the agent used, has been considered. A brief discussion relative to the possible mode of action of succinate has been presented elsewhere.<sup>3</sup>

Sodium succinate is a hexahydrated salt; therefore, the actual concentration of the solution used was about 18 per cent, rather than 30 per cent. This solution is stable at normal room temperatures (20° to 25° C.) but it becomes less effective or completely ineffective, as an analeptic, if allowed to remain at higher temperatures.

In an earlier report,<sup>3</sup> a series of 70 clinical cases that had received sodium succinate after Pentothal Sodium anesthesia ("controlled barbiturate poisoning") was compared, with a similar series that received only Pentothal. The results of that investigation demonstrated that sodium succinate when used, according to a simple procedure, was definitely effective in shortening the sleeping times of the cases in the experimental series. The results were often quite dramatic.

The purpose of the present investigation was to evaluate the effectiveness of sodium succinate used in man for the treatment of "uncontrolled" (that is, suicidal or accidental) barbiturate poisoning. The effect of the drug in 15 cases was studied. All subjects in this investigation had, or were diagnosed tentatively as having, "barbiturate poisoning"—produced accidentally *or* with suicidal intent. All were from rural areas. They were treated in a community hospital or in the home.

### METHOD

There was no specific preparation of the barbiturate poisoning cases previous to their initial treatment with sodium succinate. Manual or mechanical removal of any obstruction to the airway was a routine. When indicated, an artificial, pharyngeal or endotracheal, airway was introduced. (The endotracheal tube facilitates proper cleaning of the tracheo-bronchial tree.) The recumbent patient was placed usually in a slightly head-down position. Gastric lavage was *never* used.

Sodium succinate was given intravenously, immediately following the routine, preliminary procedures, just mentioned. The first 3 to 5 c.c. of succinate solution were injected rapidly—usually at the rate of 1 c.c. per second. The remainder of any indicated quantity was given more slowly. There is no fixed dose for sodium succinate; it should be given intermittently as indicated.<sup>3</sup>

Injection was delayed for 10 to 20 seconds after the initial dose. Typically, patients coughed once or twice during that brief pause. The cough was taken as a sign of adequate initial dose. If no cough were produced by the first dose, the dose was repeated. Unanesthetized human volunteers have described the subjective stimulus for the cough as being similar to that sensation which one experiences on taking a large drink of what he expects to be straight gingerale, but which proves to be straight whiskey!

TABLE I  
Sodium Succinate—An Analeptic for Barbiturate Poisoning in Man

Identification	No.	Sex	Age	Type and Dosage of Barbiturate	Narcosis Time			Dosage of Sodium Succinate 3 gm./10 c.c.	Narcosis Time after Succinate Therapy	T.N.T.	Comments
					Outside Hospital	Inside Hospital	Total N.T.				
42438 P. H.	1	M	61	Barbital gr. 125 (8.3 grams)	5°	42°	47°	30 gm. (100 c.c.)	15' opened eyes 45' oriented—to status quo	47°45'	Known psychopath. Negativism and bed boards on awakening.
42903 C. T.	2	F	56	None (cerebrovascular accident)	10°	3°	13°	20 gm. (200 c.c. of 10%)	30'	14°	? of cerebrovascular accident before succinate therapy. Later proved by autopsy.
47840 L. R.	3	F	58	Barbital gr. 150 (10 gm.) Nembutal, 4.5 gr.	28+1°	1°	30°	30 gm. (100 c.c.)	5" cough 2°35' oriented	32-33°	Nembutal taken with one ounce of elixir of phenobarbital. Chin relaxed on admission.
41613 P. C.	4	F	23	Seconal, gr. 19.5 (1.3 gm.)	9-10°	15'	9-10°	42 gm. (140 c.c. 3°)	4° oriented	14°	Pupils exhibit reverse reaction to light, for first 30' of succinate therapy.
39088 A. H.	5	F	66	Nembutal, gr. 13.5 (0.9 gm.) Capritol (?)	2°30'	1°	3°30'	4.5 gm. (15 c.c.)	10" cough 15' turning 20' oriented	4°	(Amyotrophic lat. sclerosis)
42225 R. D.	6	F	64	Phenobarbital (repeated doses) Amt.?	3 days ?	1 day	4 days	4.5 gm. (15 c.c.)	24° oriented	5 days	Pt. had fallen down stairs. Phenobarb. given for relief of physical discomfort (pain). Memory loss after first or second dose. "Thanks" for reviving.
42226 A. F.	7	F	45	Amytal (amount ?)	10°	7°	17°	6 gm. (20 c.c.)	10" cough 1°30' groan 3' opened eyes	17°3'	Told family she had taken "sleeping pills." They didn't believe her for 10 hours.
50427 A. H.	8	M	66	Pentothal (2.5%) (450 mg. in 15') for surg.	—	7°	7°	3 gm. (10 c.c.)	10" cough 5' tingling in face	7°5'	Normal B. P. 110/70. Before succinate 90/50. After 150/90; then in 5' to 110/70.
40560 M. S. O.	9	F	48	Sod. amytal, gr. 6 (0.4 gm.)	8°	1°	9°	3 gm. (10 c.c.)	20" cough 20' oriented	9°21'	Possible idiosyncrasy to drug or memory loss by pt. re amt. of amytal taken.
48752 P. N.	10	F	40	Phenobarbital, gr. 6.75 daily for 10 years	Semi-com.	Semi-com.	Semi-com.	3 gm. (10 c.c.)	1' (increased depth of respiration)	1°	Pt. exhibiting withdrawal symptoms of chronic barbitol poisoning.
45863 D. M.	11	F	3	Nembutal, gr. 4½ (0.3 gm.); Phenobarb.; nail polish remover.	2°45"	3°	5°45"	3 gm. (10 c.c.) Initial 15 gm. (50 c.c.) Total in 3°	2' cough 3° oriented	7-8°	Unknown amt. of phenobarb. taken. One ounce of nail polish remover (acetone).
598 A. C.	12	F	38	Nembutal, gr. 15 (1 gm.)	30'	Not in Hosp.	30'	6 gm. (20 c.c.)	15" cough 1' talking	31'	Not admitted to hospital.
47277 L. Y.	13	M	63	Seconal, gr. 27 (1.8 gm.) Divided doses.	10°	20'	10°20'	6 gm. (20 c.c.) Initial 21 gm. (70 c.c.) Total	10" cough 2° oriented	12°30'	Pharmacist. Seconal taken for relief of pain (self treatment). Could be roused but was disoriented. Memory loss.
30487	14	M	61	Pentothal (2.5%) 55 c.c. (1375 mg.) given in 15" for surgery.	—	20'	20'	2.8 gm. (9 c.c.) Initial 6 gm. (20 c.c.) Total	5' groaning 30' moving head and body	50'	Pt. in laryngospasm when succinate given. This stopped in 20".
36718	15	M	60	Pentothal (2.5%) (550 mg.) For surgery.	—	25'	25'	6 gm. (20 c.c.)	1' cough 5' eyes open	30'	Pupils pin point before succinate, dilated after 3 c.c.

° equals hour. ' equals minute. '' equals second.

While the patient was being examined, 5 c.c. of 30 per cent sodium succinate were given rapidly, by vein. After five seconds, the patient coughed and moved her right leg. Systolic blood pressure increased by 10 mm.

Three minutes after the initial injection, an additional 10 c.c. of succinate solution were given rapidly. The immediate effect was a marked increase in depth of respiration without any remarkable change in rate. The blood pressure was then 120/80.

During the first 10 minutes of therapy, the patient received 50 c.c. of succinate solution. (This was equivalent to 15 grams of hydrated sodium succinate or 9 grams of the anhydrous form.) Following this dose, the eyelid reflex was present and she was moving her legs. A crimson flush was present in the blush areas.

An intravenous clysis of 10 per cent succinate and 5 per cent glucose was started at a slow drip-rate. Fifteen minutes later, the patient was slightly cyanotic. A large amount of thick, tenacious mucus was removed from the pharynx; the infusion rate was increased; and, for five minutes, 100 per cent oxygen was given by face mask.

Two hours and 35 minutes after the start of succinate therapy, the patient was well oriented and talking coherently. She stated that she had taken "4½ grains (0.3 gram) of Nembutal, and one ounce of elixir of phenobarbital." This, certainly, was *not an excessive dose*, especially considering the fact that, according to her home physician, she was not abnormally susceptible to the usual effects of these drugs; however, two hours later, she "remembered" also 30 five-grain barbital tablets (150 grains or 10 grams) that she had taken with the other hypnotics.

This woman received 100 c.c. of 30 per cent sodium succinate (30 grams of the hydrous salt) in two hours and 35 minutes.

A three-year-old girl, who, at the time of admission, was comatose, moderately flaccid, and unresponsive to normally painful stimuli, with acetone-like breath and rapid respirations, had signs of pulmonary edema on the right. The child had no history of diabetes and, obviously, was not undernourished.

Total narcosis time before admission was indefinite, but it was not more than two and three-quarters hours.

The history of this case previous to admission was essentially as follows: The patient's five-month-old brother had been, supposedly, having his mid-morning nap. Their mother had been busy with housework until she went into the baby's room to get something. There, she found the patient "sound asleep on the floor," and the baby "wide awake in his crib." Several different types of tablets and pills were scattered on the floor; also, a new, four-ounce bottle of nail polish remover was open and only three-fourths full. The family physician was called and the patient was brought to the hospital.

Three hours after admission there had been no appreciable change in the patient's general condition. The respiratory rate remained rapid and shallow, and the child continued to be comatose and unresponsive.

At this time, 10 c.c. of sodium succinate (30 per cent) were given, in two minutes. During the initial course of the injection, the patient demonstrated the typical cough, following which she swallowed several times. A "succinate flush" appeared on her face and arms. Respirations became deeper.

Two and one-half hours later, an intravenous clysis of 10 per cent succinate and 5 per cent glucose in water was started.

Within the next half-hour, the succinate flush covered practically her entire body. The patient reacted to painful stimuli and opened her eyes, when requested to do so.

Although ataxic, she was well oriented in the following hour and asked for "a good lunch and a big glass of milk." She got both and consumed both. This was less



In several hundred administrations of sodium succinate to man, under various conditions and for various indications, there have never been visible convulsions nor production of excitement, beyond the *status quo* of the subjects concerned.

It has been stated that "patients with barbiturate poisoning fall into four groups, two of which recover and the remaining two do not. The first is the group of patients who recover without any treatment. All they require is general nursing. The second is the group of patients who die regardless of how intensive and expert the treatment is. They have simply taken so large a dose that no antidote or method of treatment can save them. The third group embraces those patients who recover only because of expert management; without the most effective measures most frequently applied they would succumb. The fourth embraces those patients who die because of the treatment."<sup>2</sup> Sodium succinate can be a factor in eliminating the last group and, probably, the second.

It may be helpful to know the amount of barbiturate a patient has taken, but this information is frequently inaccurate. It is, however, well to remember that adults are almost certain to recover, without specific treatment, from oral doses of the order of 1 or 2 grams of any of the commonly used barbiturates. The fatal dose is sometimes stated as being, in general, 15 to 30 times the therapeutic dose. It has been said that the dose of barbital which is nearly always fatal is about 10 grams, and that of phenobarbital, from 6 to 8 grams.<sup>9</sup> However, there are so many factors that may contribute to the depressing effect of the barbiturates, such as physical and mental fatigue, a very recent hot bath, analgesic drugs, etc., that discussions concerning any fixed, or even nearly fixed, so-called "fatal dose" have little, if any, value. Every case of barbiturate poisoning should be treated as an entity—regardless of drug taken, or supposedly taken. The greatest foe in the treatment of barbiturate poisoning is anoxia. The greatest foe in recovery from barbiturate poisoning may be the type of treatment employed.

A few years ago, before the use of succinate, a 17-year-old girl, who had taken an indefinite amount of phenobarbital, was admitted to our hospital. The quantity of drug concerned was estimated, by the referring physician, to be between 150 and 200 grains (10 to 13 grams). At the hospital, it was estimated that she would sleep for a week. She did.

During that entire week her position was changed every half hour, day and night, side to side, foot of bed elevated, then head of bed elevated. Some of the convulsant drugs were used, but only in relatively small doses. Supportive therapy was the main course of treatment. The maintenance of fluid, electrolyte and protein balances became a complicated problem. During the last four days of the week, a constant vigil was necessary. In order to maintain an adequate airway, it was necessary to bronchoscope the patient two or three times to remove thick, tenacious mucus from the tracheobronchial tree. Recovery was finally complete, and there were no apparent mental changes. However, it was a very exhausting ordeal, especially from the nursing standpoint. Without conscientious nursing care, recovery for this case would have been impossible. It is for cases of this type, especially, that succinate is indicated.

## BIBLIOGRAPHY

1. Federal officials puzzled by large United States consumption of sleeping pills, *Jr. Am. Med. Assoc.*, 1946, cxxxiii, 405.
2. Departments of Pharmacology and Medicine, Cornell University Medical College and the New York Hospital, Conferences. Conferences on Therapy; Treatment of Barbiturate Poisoning, *Am. Jr. Med.*, 1946, i, 93-103.
3. BARRETT, R. H.: The analeptic effect of sodium succinate on barbiturate depression in man, *Anesthesia and Analgesia*, 1947, xxvi, 74-81, 105-113.
4. DARCEY, J. F.: The picrotoxin treatment of barbiturate poisoning, *Jr. Nerv. and Ment. Dis.*, 1944, xcix, 367-375.
5. BARLOW, O. W.: The relative efficiency of a series of analeptics as antidotes to sublethal and lethal dosages of pentobarbital, chloral hydrate, and tribromethanol ("Avertin"), *Jr. Pharmacol. and Exper. Therap.*, 1935, lv, 1-22.
6. SOSKIN, S., and TAUBENHAUS, M.: Sodium succinate as an analeptic for barbiturate poisoning and in the control of the duration of barbiturate anesthesia, *Jr. Pharmacol. and Exper. Therap.*, 1943, lxxviii, 49-55.
7. CAMPBELL, C. J., MAES, J. P., and BARRETT, R. H.: Sodium succinate as an analeptic in man, *Fed. Proc.*, 1946, v, 15.
8. FITCH, R. H., and TATUM, A. L.: Duration of action of barbituric acid hypnotics as a basis of classification, *Jr. Pharmacol. and Exper. Therap.*, 1932, xlv, 325-335.
9. RICHARDS, RICHARD KOHN: The therapy of barbiturate poisoning, *In: FANTUS, BERNARD: The therapy of the Cook County Hospital*, *Jr. Am. Med. Assoc.*, 1940, cxv, 527-529.
10. ELLIOTT, K. A. C.: The possible rôle of intermediary metabolites as hydrogen carriers. *In: A symposium on respiratory enzymes*, 1942, The University of Wisconsin Press, Madison, pp. 33-35.

As Bywaters<sup>15</sup> pointed out, the disease is really not new. Similar cases had been encountered at least as early as 1909 by Colmers,<sup>23</sup> though they were not recognized. In 1946 Lucké<sup>61</sup> reported an excellent study of observations made on 538 fatal cases of "lower nephron nephrosis," as he called it.

Increased interest in and knowledge of the lower nephron syndrome and some of the acute anurias has resulted in more frequent use of the artificial kidney<sup>55, 56</sup> and other methods for the removal of toxic elements circulating in the blood of the anuric patient. Numerous papers have been published on the subject within the last few years and many more are sure to follow, especially since the possible clinical value of such procedures has been definitely realized.

### THE CLINICAL PICTURE

Before the more fundamental aspects of the lower nephron syndrome are discussed, it is advisable to review the clinical picture.<sup>16, 17, 61</sup> As stated previously, the *causative* agent varies widely. The patient suffering from a crushing injury which produces lower nephron nephrosis presents a history of having been pinned by heavy beams or pieces of masonry in such a manner that a considerable amount of tissue has been crushed. He has usually remained under the crushing force for several hours. As a rule, he appears to be in good condition soon after release except for wounds and local injuries, such as fractures and contusions. However, in a few hours he begins to show evidences of edema and slight oozing and hemorrhage into the injured tissues and from the wounds. He then passes quickly into the *first phase of shock*, which is considered by many to be due to loss of plasma through damaged capillary walls into the tissue spaces of the injured areas. These areas become extremely swollen, and the skin becomes shiny. Evidences of necrosis with bleb formation may appear. Loss of fluid into the tissue spaces results in hemoconcentration, evidenced by an increase in hemoglobin, hematocrit and erythrocyte count. During this phase of shock the skin tends to be pale, cold and moist, although the blood pressure generally remains essentially normal, apparently because of compensatory vasoconstriction. Occasionally when this vasoconstriction is not maintained, there follows a rapid drop in blood pressure, with the development of the *second phase of shock*. If plasma or fluids are administered at this time, the blood pressure will return to normal. With inadequate therapy shock may become irreversible.

The patient tends to show evidences of *anxiety*. The first or second samples of *urine* passed following the injury are noted to be bloody and to contain pigment suggestive of hemoglobin or altered hemoglobin. The urine also contains albumin, creatine, granular casts and pigment granules, which sometimes resemble intact erythrocytes. It is usually highly acid, with a pH of 4.6 to 6.0. The urine volume remains low and may even approach anuria. Oliguria continues despite fluid intake or any form of therapy. The specific gravity tends to become fixed at 1.010, correction having been made for the protein content.

known that damage to cells results in an escape of potassium into intercellular spaces.

If diuresis continues and if renal function progressively improves, the patient will make an apparently uneventful recovery. However, should diuresis fail to develop, there will ensue a continuous downward course, characterized by increasingly severe uremia with extreme mental disturbances, often terminating in coma. The patient often calls out with alarm, becomes pale, sweats profusely and the alae nasi become dilated. Death usually occurs suddenly, sometimes even within one or two minutes. He may recover from these episodes, only to be seized by another an hour or so later—one of them terminating fatally.

The general clinical pattern varies little with the responsible etiologic factors. The chief difference is in that phase of the patient's course concerned directly with the etiologic factors producing the entity. For example, in lower nephron nephrosis eventuating from a transfusion reaction there will be a history of administration of incompatible blood, followed by a severe chill and fever and then oliguria, hematuria, pigment and erythrocyte casts, and uremia, usually with ensuing death. Renal function decreases until the specific gravity is fixed at 1.010, and azotemia with retention of other toxic materials develops. In a patient who suffers a transfusion reaction, particularly postoperatively or as a result of treatment for an accident, various degrees of shock are liable to occur. *Shock* and *vomiting* are two of the associated manifestations which tend to precipitate or aggravate the oliguric state.<sup>16, 61</sup> It is interesting to note that in those patients who sustain such damage without the development of these two symptoms, the severity of the clinical state is not great.

When the lower nephron syndrome is produced by a reaction to sulfonamides, the patient has usually received the drug in the presence of an impaired cardiovascular system, such as congestive heart failure, or impaired renal function, with inadequate urinary output and often in the presence of acid urine.<sup>14, 107</sup> Hematuria occurs, associated with sulfonamide crystals in the urine and sometimes with pain over the renal regions. These patients, as a rule, do not manifest a shock-like state, although occasionally shock or peripheral circulatory collapse may occur, partially as a result of the reaction to the drug and partially as a result of the disease for which the drug was employed. The clinical course and general manifestations are essentially those described previously for the crush syndrome.

The clinical picture of the lower nephron syndrome also resembles that of the uteroplacental syndrome,<sup>109</sup> as encountered in postpartal sepsis or in criminal abortion with infection of the uterus. There is a difference in the clinical pattern due to the infection, but as far as the renal portion of the picture is concerned, it is essentially identical.

In summary, the clinical picture produced by the various disease states is modified in part by the etiologic factors concerned with the production of that

hours, depending upon the rate of development of oliguria. However, the typical manifestations do not usually appear until the last two or three days of life. Vomiting and mental disturbances, such as irrationality, drowsiness and finally coma, are commonly associated symptoms. Convulsions are rare, as in any type of true uremia.

(4) *Fatality Rate.* The fatality rate is extremely high. Once the cardinal signs of oliguria, excretion of heme pigment, azotemia and hypertension develop, it reaches about 90 per cent. The course of the disease is relatively brief, and in fatal blood transfusion reactions the survival period is usually three to 10 days. In the crush syndrome death usually occurs by the end of the first week; most patients surviving eight to nine days recover. In one series<sup>61</sup> 74 per cent of the patients died within the first 48 hours. About 8 per cent of the patients who died have been reported to survive more than 12 days. It is not known whether death is due entirely to renal damage or in part to the precipitating cause itself, but it is quite likely that there are a number of contributing factors.

#### PATHOLOGY

The organic changes, other than those which occur at the primary site of injury by the etiologic agent, such as local tissue damage in the case of the crush syndrome or injury to the gastrointestinal tract in the case of mercurial poisoning, are largely confined to the kidneys.

*Gross Appearance of the Kidneys.* There are no pathognomonic gross manifestations of the lower nephron syndrome. The essential gross and microscopic manifestations are as follows<sup>8, 15-17, 30, 61, 74, 77</sup>: The kidneys are usually swollen and increased in weight, in some instances two or more times the normal weight. There has been no definite correlation between the size of the kidneys and the duration of the disease, although a certain amount of time is required for the swelling to develop. There is some suggestion that the increase in size of the kidneys after trauma or burns tends to be greater than that following nontraumatic conditions, such as transfusion reactions. Typically the kidney is somewhat soft, the capsule strips easily, the outer surface is pale, smooth and glistening, and a clear or slightly bloody fluid oozes from the cut surface. The cortex is widened and tends to bulge perceptibly. It is moist, pale and in sharp contrast to the dusky, somewhat cyanotic-appearing medulla. The striations are often greatly accentuated. A whitish stripe has been described in the inner aspect of the cortex.

*Microscopic Findings.* The histologic descriptions, including those of Bywaters and his group,<sup>15-17</sup> Minami,<sup>74</sup> Lucké<sup>61</sup> and Mallory,<sup>69</sup> have been summarized into four essentially distinct categories by Lucké<sup>61</sup>:

(1) There is degeneration and necrosis which involves somewhat selectively the lower part of the nephrons, that is, the thick portions of the loops of Henle and the distal convoluted tubules.

These degenerative changes may result in bulging or even actual rupture of the necrotic portions into the veins. Diverticuli may be observed. Regeneration in various stages of development begins to make its appearance if survival time exceeds three or four days. There may be casting off of segments of epithelium with the growing of new cells beneath the dead lining. In the early stages the protoplasm tends to be basophilic and the nuclei stain intensely.

Healing takes place rapidly; if the patient survives 10 days, it is likely that the areas will be completely reepithelized. Casts are the most characteristic and outstanding microscopic findings; they are usually of two kinds:

(1) Most conspicuous are the pigmented masses of heme substances which are found inspissated within the lumen of the lower portions of the nephrons. These are particularly highly developed when there is destruction of muscle and apparently have their origin from myohemoglobin or some of its derivatives. In hemolytic conditions, such as transfusion reactions, hemoglobin casts develop which are similar to the myoglobin casts following destruction of muscle. In unstained sections the casts have a reddish hue; when stained with hematoxylin and eosin, they are usually brownish or copper-colored, but the reaction for iron is negative.<sup>61</sup> The casts have a smooth and solid appearance and occasionally assume the form of spherules. They tend to accumulate in greatest numbers in the distal convoluted tubules but are larger in the wider collecting tubules. When they occur near thin-walled veins, they are apt to be prominent.

(2) Less conspicuous are those casts which are not pigmented and have the appearance of hyalin casts. They are stained faintly with eosin and look much like inspissated and coagulated protein material. Tending to occur in the region of the lower nephron where the injury is most severe, they give the impression of obstructing and blocking the flow of urine through the nephron.

Another interesting aspect of the microscopic pathologic changes is that seen in the interstitial tissues around the foci in the tubules showing extreme disintegration. Edema and inflammatory reactions are evident. There is an accumulation of inflammatory cells, particularly lymphocytes and histiocytes, whereas granulocytes are scanty and giant cells are rarely seen. Fibrosis usually develops at the end of a week, and if there is a great deal of destruction, scars appear. These areas may vary from relatively few to large numbers, depending upon the severity of the reaction. The interstitial changes are particularly pronounced in the boundary zone and at times in the cortex around the venous channels near the glomeruli. If necrosis is severe, casts are extruded into the stroma, producing local reactions. As stated previously, one of the interesting pathologic changes is found in the region of the large venous channel, especially in the boundary zone. There the veins are rather thin-walled and normally course near the renal tubules. When the tubules are damaged, the veins apparently bulge into the lumen.

red cells are suddenly hemolyzed. When pigments are liberated in large quantities and cannot be metabolized in usual fashion by the liver to be excreted in the bile, they are excreted by the kidneys.<sup>2, 5, 39, 60, 72, 75, 112</sup> The mechanism by which the pigments reach the lumen of tubules is not clear. There are differences of opinion about the passage of hemoglobin molecules through the glomerular membranes. Since the molecular weight of hemoglobin is 68,000 and that of serum albumin is 70,000, it is considered by many observers to be unlikely that hemoglobin is able to pass through the glomerular membranes any more easily than serum albumin. However, several hypotheses have been presented to explain the mechanism by which hemoglobin enters the lumen of the nephron. One is that a small amount leaks through the glomeruli; a second is that some of the hemoglobin is broken into small components and is excreted as such; and a third is that damage to the tubules and glomeruli increases the permeability of these membranes to hemoglobin. None of these ideas is supported by sufficient direct data. As pointed out by Kreützer and his associates,<sup>57</sup> who reviewed the data on the excretion of hemoglobin and myoglobin in the urine in a study of spontaneous myohemoglobinuria, little is known about the details.

Myoglobin has a molecular weight of 17,500, or is about one-fourth the size of the hemoglobin molecule, and it contains one iron atom instead of four. Because of the presence of iron, the benzidine or guaiac test for occult blood in the urine of patients with myoglobinuria is positive. The diagnosis of myohemoglobinuria should be considered if the urine is dark and yields a positive test for occult blood, is free from red cells, and if no evidences of hemolytic disease exist. Since a minimum of about 20 mg. of hemoglobin per 100 c.c. of plasma has to be reached in order to give a reddish tinge to the plasma and since myoglobin has a renal threshold of about 20 mg. per 100 c.c. whereas that of hemoglobin is 100 mg., the color of the plasma aids in differential diagnosis. Therefore, it is possible to rule out hemoglobinuria, if a sample taken just before the appearance of dark urine does not exhibit a reddish tinge. Of course, myoglobin can be differentiated from hemoglobin and identified easily by means of ultracentrifugation, ultrafiltration and by spectroscopic examination. Myoglobinuria might be confused with acute porphyrinuria, but this is relatively unlikely since the porphyrins do not give a positive reaction to the benzidine or guaiac tests for occult blood. However, such problems are not troublesome in the presence of the lower nephron syndrome, since the other phases of the disease are distinct. The small size of the myoglobin molecule, the low renal threshold, and the rapid liberation of myoglobin from damaged muscle all contribute to the sudden overloading of the kidneys whenever there is crushing or damage to large masses of muscle. Apparently the low renal threshold is related to the molecular size of 17,500, which is small enough to permit passage through an unaltered glomerular membrane.

The heme compounds are apparently concentrated or precipitated in the lower part of the nephron. This is true of that derived from hemoglobin

the kidney. It has also been suggested that *organic* and *inorganic substances*, such as uric acid, phosphoric acid, potassium and creatine, liberated by injured tissue or toxic states, contribute to the renal damage.<sup>9, 35, 50, 61, 64, 96</sup>

Still others have suggested that *proteolytic enzymes* liberated in injured tissue may be responsible for the damage to the renal tubules.<sup>76</sup> Associated vomiting, disturbances in electrolyte balance, malnutrition, and dehydration may contribute to the intoxication and damage of the kidneys.<sup>15, 16, 61</sup> Disturbances in blood volume and in fluid balance could conceivably contribute to reduction in renal function, although such ideas remain conjectural.

It has also been proposed that disturbances in renal blood flow, particularly in the presence of shock, are of paramount importance in diminishing renal function and in damaging the nephron.<sup>26, 32, 54, 59, 81, 88, 93, 98, 99, 102, 103</sup> It has been observed that in patients suffering from shock, particularly if it is severe and prolonged, more severe damage to the tubules is sustained. This, however, may not be directly related to the shock, the latter being only another manifestation of the severity of the general injury. It is likely that all of the facts mentioned play some rôle, though the exact mechanism and the contributing rôle of each individual factor is not yet clear.

The mechanism by which oliguria develops is likewise unknown. Several hypotheses have been presented: (1) That it is due to a disturbance in glomerular filtration, which is the result of impairment of renal circulation.<sup>4, 29, 37, 49, 53, 67, 71, 85, 91, 92, 95</sup> This is related to the idea advanced by Trueta and his associates<sup>100</sup> of "shunting" of the renal circulation from the cortical portion of the kidneys to the medulla. It may be partially attributable to peripheral circulatory collapse and shock which impair glomerular filtration. (2) That oliguria results from tubular obstruction, which interferes with the rate of urinary flow. However, more and more observers are rejecting this concept. (3) That oliguria is incident to the disturbance in tubular reabsorption as a result of tubular damage from an impairment of renal circulation, a theory proposed by Phillips and coworkers<sup>53, 85</sup> and by others. The damaged areas, that is, the lower tubular portions of the nephron, become essentially parchment paper as far as selectivity of reabsorption is concerned.<sup>15, 16, 53, 61, 85</sup> Since there is no selective reabsorption, absorption of glomerular filtrate is complete qualitatively and almost quantitatively.<sup>87</sup> Consequently, the glomerular filtrate passes down the tubules and diffuses unaltered back into the circulation, so that there is almost complete reabsorption of the glomerular filtrate in its native state. This results in the formation of urine with approximately the same specific gravity as that of the glomerular filtrate, a value of 1.010. Lucké<sup>61</sup> and others are of the opinion that this almost complete leaking of glomerular filtrate through damaged tubular walls back into circulation is the best hypothesis to explain the histologic and clinical data of the lower nephron syndrome.

There are also many extrarenal factors concerned with the toxic picture. For example, anuria and azotemia will produce intoxication. Vomiting,



striction does not selectively involve the cortical portions of the kidney. When shock progresses so that the blood pressure reaches extremely low values, the filtration pressure is decreased and the quantity of glomerular filtrate becomes reduced. Corcoran, Taylor and Page<sup>56</sup> found a decrease in renal blood flow due almost entirely to an increase in renal vascular resistance in dogs following release of the tourniquets in "tourniquet-produced" shock. This is brought about by the increase in blood viscosity and by vasoconstriction of the afferent and efferent glomerular arterioles. Pain is of little influence, as blocking of sympathetic nerves has no effect upon renal function. Apparently, therefore, vasoconstriction is humoral in origin.

Phillips and his associates<sup>53, 85</sup> have shown that ischemia produced by gently clamping the renal arteries will interfere especially with tubular function. The main effect is to decrease selective absorption of the tubules so that glomerular filtrate is absorbed almost completely, the tubules becoming essentially parchment membranes, instead of living membranes with ability to absorb selectively. Similar observations have been made by Badenoch and Darmady.<sup>4</sup> These latter authors were able to produce disturbances in the distal segments, including patchy necrosis similar to that described by Bywaters<sup>15</sup> and Lucké.<sup>61</sup> Apparently, there was correlation between the histologic picture and disturbances in renal function.

*Sequelae.* The fatality rate is extremely high, the survival rate varying between 10 and 33 per cent. As far as is known, those who survive apparently do not experience residual disturbances in renal function, although it is not clear from published reports whether or not adequate follow-up studies have been conducted. A prolonged follow-up period would be required to ascertain the residual renal state. It is well to bear in mind when estimating morbidity that patients with the most severe damage die whereas those with the least survive; therefore, a follow-up of renal function would necessarily include only those with mild damage. With improvement in therapeutic methods, increased survival rate of the more seriously ill patient will result, thus permitting better evaluation of the problem of morbidity, particularly if follow-up studies are emphasized.

## TREATMENT

Before a discussion is undertaken of the management of the patient in whom the syndrome has developed, it is necessary to point out that there are certain types of the lower nephron syndrome which can be readily prevented. Most transfusion reactions are avoidable, being due entirely to carelessness. The same is true of intoxications, especially sulfonamides; more care in the selection of patients and during administration should reduce the incidence of injury from sulfonamides. Furthermore, when the slightest evidence of damage appears, immediate discontinuance of these drugs will usually result in minimal injury. It is the neglected patients who sustain the greatest damage. Uteroplacental damage with the complicating lower nephron syn-

The rôle of sympathetic blocking or sympathectomy is yet to be evaluated. Amputation should be performed if the part is definitely useless but unless it is done within the first 24 hours, postponement may be necessary, particularly if renal damage is serious.<sup>16</sup> Under such conditions, splinting and physical therapy should be employed until amputation can be performed.

Once renal failure, with oliguria and progressive uremia, develops, relatively little can be done except for the use of some of the more experimental procedures now under investigation, such as the artificial kidney or dialysis. It has been suggested that fluids should be administered to these patients in the presence of anuria and oliguria. However, it is well to remember that large quantities of fluids may produce severe edema and increase the damage. Sodium lactate, 5 per cent glucose, and sodium chloride may be used in amounts governed as much as possible by studies of the blood chemistry and by the clinical state. Human Ringer's solution may also be used. It is possible to administer fluids by means of gastric or duodenal tubes if the patient is not vomiting excessively; otherwise, intravenous medication must be employed. Fluids should not be administered to any extent beyond that which produces slight edema; in these amounts fluids might dilute the toxins and at the same time produce diuresis once renal function begins. Mercurial diuretics and decapsulation have been advocated, but it is unlikely that the latter is of any value. If results are not obtained promptly with mercurial diuretics, they should be discontinued. However, in view of the nature of the lesions and the mechanism of action of mercurials, it is likewise unlikely that these would be of great value—in fact, actual increased damage might result. One or two doses will probably be accompanied by no deleterious effects.

*The Artificial Kidney.* There has been increased interest in the use of artificial methods for eliminating metabolites. These procedures are based upon the principle that a method, even if crude, which would eliminate toxic substances during acute renal failure might prolong life long enough to permit renal repair and return of renal function. This idea is not a new one; it was advocated as early as 1923.<sup>44, 52, 70</sup> A number of papers have been published suggesting this procedure or peritoneal lavage: that of Ganter<sup>44</sup> in 1923, Landsberg and Gnoinski<sup>58</sup> in 1925, Rosenak and Siwon<sup>90</sup> in 1926, Bliss, Kastler and Nadler<sup>11</sup> in 1932, Haam and Fine<sup>51</sup> in 1932, Rhoads<sup>80</sup> in 1938, Balazs and his associates<sup>6</sup> in 1934, Wear, Sisk and Trinkle<sup>106</sup> in 1938, Fine, Frank and Seligman<sup>40</sup> in 1946, Buckley and Scholten<sup>13</sup> in 1947, and Basset and coworkers<sup>7</sup> in 1947.

The method of peritoneal lavage consists in placing a catheter in an upper lateral abdominal quadrant and another in the lower contralateral abdominal quadrant and running a large quantity of a modified Tyrode's solution through the peritoneal cavity. This is done continuously, 18 to 24 liters being used in 24 or 48 hours. The formulae for these solutions may be found in the aforementioned papers describing the technic. These solutions have sulfadiazine, heparin, and penicillin added in order to prevent

triple-bore, thin-walled rubber tube with a small balloon at its tip. In experimental animals, the tube was passed various distances down the intestinal tract, the balloon was inflated and the intestinal tract was irrigated with the perfusion fluid. Warm physiologic saline solution was used. The observers were able to reduce azotemia from 198 to 126, from 198 to 112, from 231 to 145 mg. per 100 c.c. in separate animals, using 12 to 18 liters of fluid over a period of about six hours. They found that the return rinsing fluid contained from 4.3 to 5.4 gm. of nonprotein nitrogen. This idea is essentially the same as gastric lavage but should be more promising because of the more rapid diffusion of materials and greater diffusion areas. Further investigations are definitely indicated.

As indicated by all investigators, if the patient survives the period of acute uremia and the acute disease so that repair may take place, diuresis would be established in many severely injured patients. The percentage of patients who sustain serious damage and who will again produce urine is undetermined. There must be some limit to the degree of damage and the ability for repair. Postmortem studies have indicated that if some of the patients had been able to survive a few more days, it is likely that renal function would have returned to normal. The therapeutic problem is to prolong life during a brief critical period. General hospitals with proper laboratory facilities and trained personnel should be prepared to employ the new procedures previously described, which promise to be life saving.

*General Therapeutic Measures.* It is important to remember that certain general measures must be emphasized in the management of these patients. Most important of all is *good nursing*. The patient should have constant attention, particularly when he is having his greatest difficulty. He should be made mentally as well as physically comfortable, since he is apt to become apprehensive and anxious about his disease. Most patients know they are seriously ill and are aware of the fact that they are likely to die.

Attention to electrolyte balance, fluids, vitamins, and nutrition should be emphasized. If possible, a large portion of the necessary fluids and carbohydrates should be given by gastric or duodenal tube. Protein intake should be held to a minimum during the time of renal failure, for the metabolism of administered proteins will only increase the rate of accumulation of non-protein nitrogen and toxic protein substances.

Borst<sup>12</sup> has found that a diet low or absent in protein, consisting almost entirely of fat and carbohydrate, is of considerable value in the management of acute renal insufficiency. Some of his patients were fed a diet consisting of 150 gm. of butter and 200 gm. of sugar, a total of 2,000 calories. This yields practically no protein and little potassium and phosphorus. Patients have received this diet for over three consecutive weeks, except for variations in quantity, without difficulty and with great benefit during periods of uremia. Contrary to most opinions, severe-to-complete restriction of proteins in the diet reduces protein catabolism to extremely low levels, so that by the end of three days the daily nitrogen excretion is less than 6 gm., and

15. BYWATERS, E. G. L.: War medicine series; crushing injury, *Brit. Med. Jr.*, 1942, ii, 643-646.
16. BYWATERS, E. G. L.: Ischemic muscle necroses; crushing injury, traumatic edema, the crush syndrome, traumatic anuria, compression syndrome: a type of injury seen in air raid casualties following burial beneath debris, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 1103-1109.
17. BYWATERS, E. G. L., and BEALL, D.: Crush injuries with impairment of renal function, *Brit. Med. Jr.*, 1941, i, 427-432.
18. BYWATERS, E. G. L., DELORY, G. E., RIMINGTON, CLAUDE, and SMILES, JOHN: Myohemoglobin in the urine of air raid casualties with crushing injury, *Biochem. Jr.*, 1941, xxxv, 1164-1168.
19. BYWATERS, E. G. L., and DIBLE, J. H.: Renal lesion in traumatic anuria, *Jr. Path. and Bact.*, 1942, liv, 111-120.
20. BYWATERS, E. G. L., and DIBLE, J. H.: Acute paralytic myohaemoglobinuria in man, *Jr. Path. and Bact.*, 1943, lv, 7-15.
21. BYWATERS, E. G. L., and STEAD, J. K.: Production of renal failure following injection of solutions containing myohaemoglobin, *Quart. Jr. Exper. Physiol.*, 1944, xxxiii, 53-70.
22. BYWATERS, E. G. L., and others: Discussion on the effects on the kidney of trauma to parts other than the urinary tract, including crush syndrome, *Proc. Roy. Soc. Med.*, 1942, xxxv, 321-339.
23. COLMERS, DR.: Ueber die durch das Erdbeben in Messina am verursachten Verletzungen, *Arch. f. klin. Chir.*, 1909, xc, 701-747.
24. CORCORAN, A. C., and PAGE, I. H.: Effects of hypotension due to hemorrhage and of blood transfusion on renal function in dogs, *Jr. Exper. Med.*, 1943, lxxviii, 205-224.
25. CORCORAN, A. C., and PAGE, I. H.: Renal damage from ferroheme pigments, myoglobin, hemoglobin, hematin, *Texas Rep. Biol. and Med.*, 1945, iii, 528-544.
26. CORCORAN, A. C., TAYLOR, R. D., and PAGE, I. H.: Immediate effects on renal function of the onset of shock due to partially occluding limb tourniquets, *Ann. Surg.*, 1944, cxviii, 871-886.
27. DAMON, S. R.: Food infections and food intoxications, 1928, Williams and Wilkins Co., Baltimore.
28. DANIELS, W. B., LEONARD, B. W., and HOLTZMAN, S.: Renal insufficiency following transfusion; report of 13 cases, *Jr. Am. Med. Assoc.*, 1941, cxvi, 1208-1215.
29. DARMADY, E. M.: Renal anoxia and the traumatic uraemia syndrome, *Brit. Jr. Surg.*, 1947, xxxiv, 262-271.
30. DARMADY, E. M., SIDMONS, A. H. M., CORSON, T. C., LANGTON, C. D., VITEK, Z., BADENOCH, A. W., and SCOTT, J. C.: Traumatic uraemia, reports on 8 cases, *Lancet*, 1944, ii, 809-812.
31. DEGOWIN, E. L., WARNER, E. D., and RANDALL, W. L.: Renal insufficiency from blood transfusion; anatomic changes in man compared with those in dogs with experimental hemoglobinuria, *Arch. Int. Med.*, 1938, lxi, 609-630.
32. DOLE, V. P., EMERSON, J., JR., PHILLIPS, R. A., HAMILTON, P., and VAN SLYKE, D. D.: The renal extraction of oxygen in experimental shock, *Am. Jr. Physiol.*, 1946, cxlv, 337-345.
33. DOUGLAS, J. W. B.: Incidence of signs of renal injury following prolonged burial under debris in an unselected series of 764 air-raid casualties admitted to hospital, *Brit. Jr. Urol.*, 1945, xvii, 142-147.
34. DUNN, J. S., HAWORTH, A., and JONES, N. A.: Pathology of oxalate nephritis, *Jr. Path. and Bact.*, 1924, xxvii, 299-318.
35. DUNN, J. S., and POLSON, C. J.: Experimental uric acid nephritis, *Jr. Path. and Bact.*, 1926, xxix, 337-352.
36. EDWARDS, J. G.: The renal tubule (nephron) as affected by mercury, *Am. Jr. Path.*, 1942, xviii, 1011-1027.

60. LOUW, ASGER, and NIELSEN, HOLGER E.: Paroxysmal paralytic hemoglobinuria, *Acta med. Scandinav.*, 1944, cxvii, 424-436.
61. LUCKÉ, B.: Lower nephron nephrosis, *Mil. Surg.*, 1946, xcix, 371-396.
62. LUETSCHER, J. A., JR., and BLACKMAN, S. S., JR.: Severe injury to kidneys and brain following sulfathiazole administration; high serum sodium and chloride levels and persistent cerebral damage, *Ann. Int. Med.*, 1943, xviii, 741-756.
63. LUND, C. C., GREEN, R. W., TAYLOR, F. H. L., and LEVENSON, S. M.: Burns, collective review, *Internat. Abstr. Surg.*, 1946, lxxxii, 443-478, in *Surg., Gynec. and Obst.* (June) 1946.
64. MCFARLANE, D.: Experimental phosphate nephritis in rat, *Jr. Path. and Bact.*, 1941, iii, 17-24.
65. MCLETCHIE, N. G. B.: Renal lesions in case of excessive vomiting, *Jr. Path. and Bact.*, 1943, iv, 17-22.
66. MAEGRAITH, B. G., and FINDLAY, G. M.: Oliguria in blackwater fever, *Lancet*, 1944, ii, 403-404.
67. MAEGRAITH, B. G., HARVARD, R. E., and PARSONS, D. S.: Renal syndrome of wide distribution induced possibly by renal anoxia, *Lancet*, 1945, ii, 293-296.
68. MALAMUD, N., HAYMAKER, W., and CUSTER, R. P.: Heat stroke; clinicopathologic study of 125 fatal cases, *Mil. Surg.*, 1946, v, 397-449.
69. MALLORY, T. B.: Hemoglobinuric nephrosis in traumatic shock, *Am. Jr. Clin. Path.*, 1947, xvii, 427-443.
70. MANN, F. C.: Peripheral origin of surgical shock, *Bull. Johns Hopkins Hosp.*, 1914, xxv, 205-212.
71. MARSHALL, E. K., JR., and CRANE, M. M.: The influence of temporary closure of the renal artery on the amount and composition of the urine, *Am. Jr. Physiol.*, 1923, lxi, 387-403.
72. MASON, J. B., and MANN, F. C.: Effect of hemoglobin on volume of kidney, *Am. Jr. Physiol.*, 1931, xcvi, 181-185.
73. MILLIKAN, G. A.: Muscle hemoglobin, *Physiol. Rev.*, 1939, xix, 503-523.
74. MINAMI AUS TOKIO, DR. SEIGO: Über Nierenveränderungen nach Verschüttung, *Virchow's Arch. f. path. Anat.*, 1923, ccxlv, 247-267.
75. MINETT, F. C.: Haemoglobinurias and myoglobinurias of animals, *Proc. Roy. Soc. Med.*, 1935, xxviii, 672-678.
76. MIRSKY, I. A., and FREIS, E. D.: Renal and hepatic injury in trypsin "shock," *Proc. Soc. Exper. Biol. and Med.*, 1944, lvii, 278-279.
77. MURPHY, F. D., KUZMA, J. F., POLLEY, T. Z., and GRILL, J.: Clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, *Arch. Int. Med.*, 1944, lxxiii, 433-443.
78. MURRAY, GORDON, DELORME, EDMUND, and THOMAS, NEWELL: The artificial kidney, *Jr. Am. Med. Assoc.*, 1948, cxxxvii, 1596-1599.
79. NECHELES, HEINRICH: Über Dialysieren des Stromenden Blutes am Lebenden, *Klin. Wchnschr.*, 1923, ii, 1257.
80. OLIVER, JEAN: When seeing is believing, *Stanford Med. Bull.*, 1948, vi, 7-12.
81. OLSON, W. H., WALKER, L., and NECHELES, H.: Study of anuria in experimental shock, *Proc. Soc. Exper. Biol. and Med.*, 1944, lvi, 64-67.
82. PAGE, I. H.: Occurrence of vasoconstrictor substance in blood during shock induced by trauma, hemorrhage and burns, *Am. Jr. Physiol.*, 1943, cxxxix, 386-398.
83. PAGE, I. H., and ABELL, R. G.: State of vessels of mesentery in shock produced by constricting limbs and behavior of vessels following hemorrhage, *Jr. Exper. Med.*, 1943, xxvii, 215-232.
84. PAXSON, N. F., GOLUB, L. J., and HUNTER, R. M.: Crush syndrome in obstetrics and gynecology, *Jr. Am. Med. Assoc.*, 1946, cxxxi, 500-504.
85. PHILLIPS, R. A., and HAMILTON, P. B.: Effect of 20, 60 and 120 minutes of renal ischemia on glomerular and tubular function, *Am. Jr. Physiol.*, 1948, clii, 523-530.

# NECROSIS OF RENAL PAPILLAE\*

By EDWARD D. ROBBINS, M.D., *Chicago, Illinois*, and ALFRED ANGRIST, M.D., *Long Island, New York*

## INTRODUCTION

NECROSIS of the renal papillae is a curious and striking lesion which most pathologists meet only occasionally at the autopsy table. The purpose of this presentation is to report briefly the cases of this disease seen at the Queens General Hospital, to discuss some of the theories of its pathogenesis, and more particularly, to relate this lesion to a similar one produced in the experimental animal by a dietary deficiency of certain fatty acids.

*Necrosis of Renal Papillae in Man.* The literature concerning this lesion, which is variously known as renal papillitis, medullary necrosis, papillitis necroticans, necrotizing renal papillitis, etc. has recently been reviewed in detail by Edmondson, Martin, and Evans.<sup>1</sup> These authors have traced the first case report back to 1877, but Gunther<sup>2</sup> in 1937 first emphasized the frequent association of diabetes with this lesion.

Approximately 110 cases were reported in the literature up to 1947,<sup>1, 4, 5</sup> and of these, 62 had diabetes and 48 did not; of the latter, 85 per cent had urinary tract obstruction. From the large series reported by Edmondson et al.<sup>1</sup> and by Robbins, S. L., Mallory and Kinney,<sup>5</sup> it is apparent that 12 to 20 per cent of diabetics coming to autopsy have acute pyelonephritis. Of these, 25 per cent have necrosis of the papillae. Hence the lesion may be found in 3.2 to 5 per cent of all diabetics. In contrast, 3.3 per cent of non-diabetics coming to autopsy have acute pyelonephritis. Of these, 2 per cent have necrosis of the papillae. Hence the lesion may be found in only 0.06 per cent of non-diabetics. The overall incidence of the disease in pyelonephritis is about 4 per cent.<sup>1</sup> Robbins, Mallory and Kinney found that in 74 per cent of their cases, death was attributable directly to the papillary necrosis.

The great majority of non-diabetics who have papillary necrosis have some obstruction of the urinary tract. This was present in six out of seven cases in one series,<sup>5</sup> in 20 out of 21 cases<sup>1</sup> in another; and in five out of six of our cases. Benign hypertrophy of the prostate is the usual cause, but carcinoma of the prostate, urethral stricture, "cord" bladder and renal calculi have also been found.

The variation in sex incidence is also striking. In diabetics, the ratio of females to males is 2:1; in non-diabetics the ratio of females to males is 1:6, due to greater frequency of urinary tract obstruction in males, chiefly

\* Received for publication October 14, 1948

The Transactions of the New York Pathological Society contain an abstract of this paper, together with discussion.

was virtually fat-free. This diet consisted of sucrose, casein which was carefully purified and rendered fat free by ether extraction, McCallum's salt mixture, ether extracted yeast for the vitamin B complex, the non-saponifiable matter from cod liver oil for vitamins A and D, and in later experiments the non-saponifiable matter from wheat germ oil for vitamin E.

Rats fed such a diet from the day of weaning develop (1) a lesion of the tail characterized by scaliness, inflammation, swelling, and later necrosis of the tip, (2) redness, swelling and scaliness of the feet, (3) dandruff and loss of body hair, (4) cessation of growth, (5) bloody urine. The animals maintained a plateau of the weight curve for weeks and months, then declined in weight and died. At autopsy, five of the eight animals had abnormal kidneys. It was felt that the immediate cause of death was kidney degeneration.

The addition of 10 drops of lard daily to the diet of these diseased animals produced a prompt cure of all lesions and a gain in weight; while the addition of 2 per cent of the total diet as lard from the beginning of the experiment completely protected the animal from the disease. Furthermore, the addition of pure glycerol, or the non-saponifiable matter from lard did not protect against the disease, but 13 drops of the fatty acid fraction from lard did give protection. Feeding 200 mg. per day of the fatty acid fraction of lard to a diseased rat on the fat free diet produced a 2 gram/day increase in weight, a tenfold effect.

They demonstrated by a series of experiments that (1) the disease is not due to a deficiency of vitamins A, B, D or E; (2) the fat free yeast, and the non-saponifiable matter from cod liver oil, and from wheat germ oil, were adequate sources of these vitamins and that (3) these latter substances were absorbed in the absence of fat in the diet. By feeding oils of various composition with regard to saturated and unsaturated fatty acids, it was shown that cures could only be effected by unsaturated fatty acids, and of these, only linoleic or acids of higher unsaturation. Oleic acid, and saturated fatty acids were without effect. The authors concluded that warm blooded animals cannot synthesize appreciable quantities of linoleic acid, or more unsaturated fatty acids.

Later experiments<sup>8</sup> demonstrated that (1) the respiratory quotient of rats with the fat deficiency disease rises above unity after carbohydrate feeding, indicating the formation of fat from carbohydrate, but the persistence of the disease proves that linoleic or other more unsaturated fatty acids are not formed.<sup>9</sup> (2) The highly unsaturated fatty acids of cod liver oil can be used by fat deficient rats for growth, but the skin lesions can only be cured by linoleic or linolenic acids, which are lacking in cod liver oil.<sup>10</sup> (3) Feeding pure fatty acids as the methyl esters proves again the complete ineffectiveness of oleic acid, the curative value of linoleic and linolenic acids, and the ineffectiveness of alpha eleostearic acid, an isomer of linolenic acid.<sup>11</sup> (4) The scaly skin and tail necrosis in this disease are not a symptom com-

with fat deficiency disease, in which cures were attempted with various inadequate fats, the same changes were noted as above. However, calcification of the papilla and apical necrosis were present in one rat of nine. In a group of rats in whom the deficiency disease was first induced, and then cured by the addition of lard to the diet, the kidneys were normal grossly and microscopically. Another group of 35 rats with the fat deficiency disease was treated with various fats including linseed oil, corn oil, olive oil, etc. At autopsy, the general condition was fair to good, the animals being only 10 per cent underweight on an average. However, degenerative changes and calcification of cortical tubule cells were widespread. Degeneration of papillary ducts was found in 21 cases, with calcification and necrosis of the papillae in seven of the 21. The necrotic areas were smaller than those found in the first group.

Thirty-eight rats, which were fed diets containing lard, or a regular stock diet, were used as the controls.

These authors concluded that characteristic renal lesions were present in rats fed on a diet free of fat but otherwise adequate. The most striking lesion was calcification of tubules and necrotic areas in the renal medulla, with disintegration of the apex of the pyramid in some. The addition of lard to the diet prevented the renal lesion, or cured it to a large extent.

### MATERIAL

Fourteen cases of papillary necrosis which were autopsied at the Queens General Hospital, are described below. These include 13 acute cases, and one which was healed. Eight of these cases were diabetics and six non-diabetics.

### DIABETIC CASES

Seven acute cases, and one with healed papillitis were found in diabetics. (The latter will be discussed separately.) There were six females, and two males, in an age range from 42 to 79 years, with an average age of 57. Two patients were admitted to the hospital in coma, and one was stuporous. Three patients died in 18 hours or less after entering the hospital. Two of these had 3 to 4 plus glycosuria, but no acetone; yet both were thought to be in diabetic coma. The shortest total duration of illness from the first symptoms was 3.5 days. The urine was abnormal in all the acute cases, though only three were noted to have pyuria. In the three acute cases in which blood urea levels were done, all had marked azotemia. In the four cases in which the hemoglobin was reported, it varied from 8.5 to 10.5 grams, with red cell counts between 3 and 3.5 million. Three had unilateral papillary necrosis, and two showed unilateral pyelonephritis.

The single male patient in the acute cases had benign prostatic hypertrophy with urinary retention and a cystotomy was performed during his hospital course.



At autopsy, the kidneys contained multiple cortical abscesses, with a perirenal abscess on the left. Necrosis of the papillae was present in the left kidney. The pelves and ureters were dilated and revealed ecchymoses. There was a bullous hemorrhagic cystitis. Microscopy revealed advanced papillary necrosis (figures 1 and 2).

*Case 2.* This 57 year old Negro female was admitted in coma. The past history was not known, but she was reported to have been "sick" for eight days. On physi-



FIG. 2. Micro-photograph showing junction zones between necrotic tissue of papilla and viable tissue with inflammatory reaction in between.

cal examination, she was in deep coma, dehydrated, hyperpneic, and had an acetone odor on the breath. Temperature 102°.

Laboratory data: Urine: milky; glucose 4 plus, acetone 3 plus; loaded with pus cells and pus casts. Six hours later, after she had received 725 units of insulin, three liters of Hartman's solution, and intravenous sulfadiazine, the glycosuria fell to 1 plus, the acetonuria disappeared, and she showed signs of returning consciousness. She

Laboratory data: Urine: Albumin 3 plus; glucose 2 plus; microscopically negative; Hb. 9.5 gm.; red blood cells 3.29 millions; white blood cells 7650. Blood sugar 315 mg. per cent.

She developed an abscess of the buttock, which was incised and drained. She ran a spiking temperature, deteriorated rapidly, and died on the eleventh post operative day (the fifty-first hospital day).

Clinical diagnosis: Diabetes mellitus; arteriosclerotic heart disease; abscess of buttocks; bronchopneumonia.

At autopsy, the kidneys were large, pale, and contained many cortical abscesses. There was bilateral renal papillitis, bilateral ureteritis, and cystitis. Microscopy showed circumscribed areas of typical necrosis of the renal papillae.

*Case 6.* This 43 year old, white female had fractured the right hip 10 weeks previously. After three weeks at another hospital, she was sent home where she began to vomit continuously for the next two weeks. For the past 12 days the urine had been bloody, and there had been a bloody stool on the day of admission. The past history included treatment for lues and known diabetes for 14 years.

Physical examination revealed a stuporous pale patient, with Argyll-Robertson pupils, absent knee and ankle jerks; and blood pressure 80 mm. Hg systolic and 60 mm. diastolic.

Laboratory data: Urine—albumin 2 +, glucose 0, acetone 0, micro-clumps of pus cells and many red blood cells. Hemoglobin 8 gm., white blood cells 15,200 with 88 per cent polynuclears. Blood urea 170 mg. per cent. Blood sugar 140 mg. per cent.

Cystoscopy revealed a necrotizing cystitis with involvement of the trigone. The blood urea fell to 85 mg. per cent but CO<sub>2</sub> combining power was found to be 33 vol. per cent. Culture of the bladder: *B. coli* and *Streptococcus non-hemolyticus*. The white blood count rose to 30,700 with 89 per cent polynuclears. The urines were maintained sugar free. She died on the tenth hospital day.

Clinical Diagnosis: Diabetes mellitus; necrotizing cystitis; acute pyelonephritis.

At autopsy the kidneys were large and smooth. All the renal papillae showed yellowish necrosis. There was an acute ureteritis and a severe hemorrhagic cystitis. Microscopy revealed an advanced papillary necrosis.

*Case 7.* This 52 year old white female was admitted with a six hour history of aphasia and weakness of the legs. She had complained of being "sick" for the previous three days but the nature of her complaints was not known. She had complained of headaches, dizziness and nocturia for the past year.

Physical examination revealed an obese, aphasic patient with a temperature of 99.2°. There was no paralysis of the extremities, but the left naso-labial fold was flattened. The plantar reflexes were normal.

Laboratory data: Urine—glucose 4 plus, acetone 0, no casts, microscopically negative.

Her temperature rose rapidly to 105.4°. She died 17 hours after admission.

Clinical diagnosis: Cerebrovascular accident; diabetes mellitus.

At autopsy the papillae of both kidneys were necrotic. The pelves were injected; the ureters and bladder were unremarkable. There were no areas of hemorrhage or softening in the brain. On microscopy the necrosis of the papillae was advanced.

*Case 8.* This 79 year old white male was admitted from a convalescent home. One month previously his right leg had been amputated for gangrene. He was a known diabetic, regulated by diet alone. On admission he was pale and disoriented. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. The heart was enlarged. Basal râles were present in both lungs. The prostate was 3 plus enlarged, hard, nodular and non-tender. There was a right mid-thigh amputation stump.

Clinical diagnosis: Hypertensive and arteriosclerotic heart disease III C; diabetes mellitus; anemia.

At autopsy the left kidney was unremarkable except for a 2 cm. cortical adenoma. The right kidney was unremarkable except for the papillae, which were atrophic and fibrotic. The pelvis was not dilated. The ureters were patent. The bladder showed moderate trabeculation, but no evidence of inflammation. Microscopy revealed healed renal papillitis of the right kidney (figure 3).



FIG. 4. Note hydronephrosis resulting from absorption of necrotic papillae in the upper-most and lower-most calyces.

Case 8 with healed papillary necrosis, deserves special mention. He was an elderly diabetic who had had an amputation of the right leg one month before admission. The urine was negative and the blood urea nitrogen was not elevated. He died on the eleventh hospital day of a severe broncho-

benign hypertrophy and two carcinomas of the prostate). Four of the five had prostatic operations during their hospital stay. All had azotemia. All were moderately anemic, with hemoglobins ranging from 8.5 to 11 grams, and red cell counts from 3 to 4 million. Pyuria was found in four cases, and hematuria in four cases (two gross, two microscopic).

At autopsy all had extensive upper and lower urinary tract inflammatory disease, with cystitis, ureteritis and bilateral pyelonephritis. Only two of the six had advanced necrosis of the papillae—the others revealed limited areas of necrosis within the papillae in areas of acute pyelonephritis.

The lone female had striking bilateral advanced papillary necrosis, but only a moderate urinary tract infection. She had, in addition, a fractured skull, portal cirrhosis and jaundice. The urine was reported sugar free, but a blood sugar was found to be 186 mg. per cent so that this case may well belong to the diabetic group.

#### CASE REPORTS

*Case 1.* This 73 year old female fell at home and struck her head. One week later she developed nose bleeds, and jaundice, and was admitted to the hospital. The skin and sclerae were icteric. The liver was palpable one finger's-breadth below the costal margin. Roentgenograms of the skull revealed a fracture in the mastoid region probably extending to the base.

Laboratory data: Urine: albumin 2 +, glucose 0, 12 red blood cells per high power field, and 10 white blood cells per high power field. There were no clumps or casts. Hemoglobin 10.5 gm.; red blood cells 3.4 millions; white blood cells 31,100 with 87 per cent polynuclears. Non-protein nitrogen 162 mg. per cent. Blood sugar 186 mg. per cent.

She became comatose, incontinent, and developed projectile vomiting and tarry stools. Her temperature varied from 99° to 101°. She died on the seventh hospital day.

At autopsy the kidneys revealed advanced bilateral papillary necrosis. The microscopic sections demonstrated the classical histology of advanced papillary necrosis (figure 6).

*Case 2.* This 74 year old white male entered the hospital because of difficulty in urinating during the preceding month. Two weeks before admission he had complete retention and was catheterized on several occasions. On rectal examination, the prostate was enlarged (grade 2), but not hard.

Laboratory data: Urine on admission—albumin 2 plus, glucose 0, microscopically negative. Later specimens were grossly bloody, and contained pus cells. Hemoglobin 8.5 gm., red blood cells 3.1 millions. The blood urea was 15 mg. per cent.

A one stage perineal prostatectomy was performed. Three weeks after operation, necrosis of the anterior rectal wall and the operative site occurred. His condition deteriorated, the blood urea rose to 50 mg. per cent, and he died on the fiftieth hospital day.

Clinical diagnosis: Post-operative perineal prostatectomy with necrosis of anterior rectal wall, sepsis and anemia; arteriosclerotic heart disease.

At autopsy there was a marked bilateral suppurative pyelonephritis, an acute ureteritis, and a hemorrhagic cystitis. On microscopic section the renal papillae showed small circumscribed areas of necrosis of characteristic form.

*Case 3.* A 78 year old white male entered the hospital with complaints of difficulty in urinating (frequency, nocturia, dysuria) for one month. Rectal examination revealed a fixed, irregular, hard prostate. Temperature 100.2°.

Clinical diagnosis: Benign prostatic hypertrophy; uremia.

At autopsy, bilateral suppurative pyelonephritis, with ureteritis and gangrenous cystitis, was disclosed. Microscopy revealed small areas of non-reactive central necrosis within the papillae.

*Case 5.* This 77 year old white male entered the hospital with the history of progressive swelling of both legs, which spread to involve the scrotum and abdomen. Dyspnea and orthopnea had been present for the preceding nine months. He had frequency and nocturia. There was no history of diabetes.

Physical examination: Blood pressure 130 mm. Hg systolic and 80 mm. diastolic. The heart was not enlarged, but was fibrillating. Ascites was present. The liver was palpable two fingers below the costal margin. There was 4 plus pitting sacral and leg edema.

Laboratory data: Urine—albumin 0, glucose 0, 40 red blood cells per high power field. Blood urea 29 mg. per cent, blood sugar 125 mg. per cent.

He developed urinary retention which required an indwelling catheter. A spiking fever developed. He was given sulfa drug in small doses. On the nineteenth hospital day sulfa crystalluria with many white blood cells and red blood cells was found. The blood urea rose to 31 mg. per cent. A cystotomy was performed. His condition improved, and he became ambulatory. The blood urea on the thirty-sixth hospital day was 17 mg. per cent. A trans-urethral resection was performed. Following this he developed a shaking chill. Plasma (200 c.c.) was given. The next day he was jaundiced. The blood urea rapidly rose to 65 mg. per cent and then to 124 mg. per cent with 13.6 mg. per cent creatinine. The icteric index was 50. He died on the forty-fifth hospital day.

At autopsy, the kidneys contained multiple abscesses in the cortex. Microscopic sections revealed small areas of necrosis within the papillae, with only marginal reaction.

*Case 6.* This 81 year old white male was admitted to the hospital because of urinary retention with overflow incontinence. He had had symptoms of prostatism for five years, which had become markedly aggravated within the previous two months (frequency, nocturia, weak stream, etc.).

Physical examination: The bladder was palpated up to the umbilicus. The prostate was 1 plus enlarged, but soft.

Laboratory data: First urine—grossly bloody, albumin 2 plus, glucose 0, blood urea 17 mg. per cent.

A two stage suprapubic prostatectomy was performed. He ran a febrile course. The urine continued to show 2 plus albumin, and white cells. Blood urea rose to 34 mg. per cent. He died on the fifty-second hospital day.

Clinical diagnosis: Benign hypertrophy of prostate; hydronephrosis; pyelonephritis.

Autopsy disclosed multiple cortical abscesses in the kidneys. Papillary necrosis was noted bilaterally. The microscopic sections revealed small areas of necrosis within the pyramids.

### THEORIES OF PATHOGENESIS

A variety of theoretical explanations of the pathogenesis of necrosis of the renal papilla has been advanced.

*I. The Rôle of Infection.* It is at once apparent that all of the cases occur in association with active pyelonephritis, which is usually suppurative. The toxins of bacteria,<sup>2</sup> the coagulase and necrosin of *Staphylococcus aureus*,<sup>1</sup> and the toxic metabolic products of *B. coli*<sup>18</sup> have all been suggested as factors in the production of the lesion. However, the multiplicity of the bac-

*III. Mechanical Factors.* Robbins, S. L., et al.<sup>5</sup> state that papillary ischemia best explains the occurrence of papillary necrosis. They suggest that the marked inflammatory reaction in the diabetics, and the back pressure of urinary tract obstruction, both operate to further mechanically reduce the anatomically inferior blood supply to the papillae by compression of the

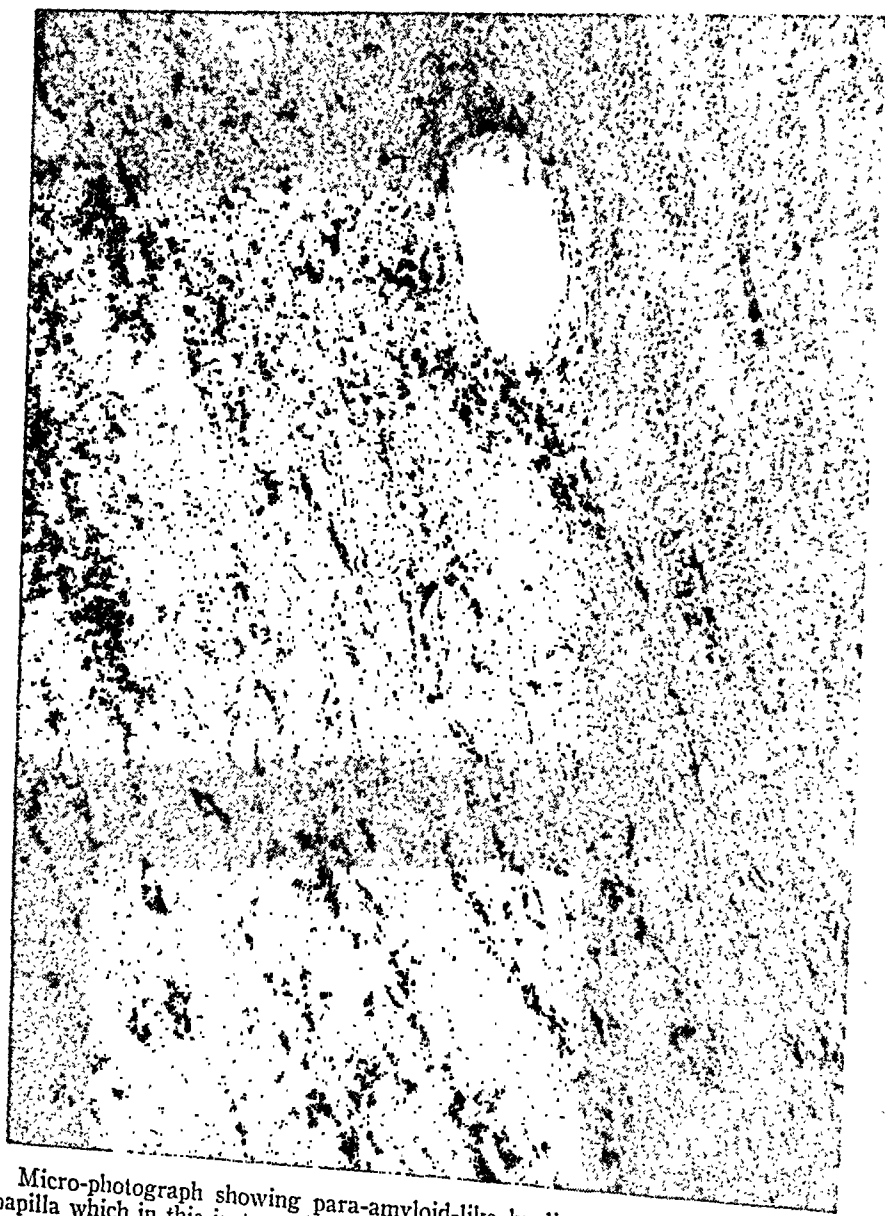


FIG. 7. Micro-photograph showing para-amyloid-like hyalin material in the stroma of the papilla which in this instance bears no direct relationship to necrosis of papillae.

thin wall capillaries. Davson and Langley<sup>18</sup> also discuss the rôle of mechanical pressure, and question why, if pressure on blood vessels were the cause of the necrosis, the lesion is not more often seen in hydronephrosis or nephrolithiasis. Mellgren and Redell<sup>26</sup> consider the deposition of the "para-amyloid" in the interstitial tissue of the renal papillae to play a

of the pyramid with distal ischemic infarction, as described by Robbins, S. L., Mallory and Kinney.

Comparison with necrosis of the papillae produced by chemical poisons<sup>23, 24</sup> confirms the above interpretation, that the lesion is produced by death of tissue en masse, followed by a variable amount of reactive inflammation and bacterial proliferation. Certain specific chemical poisons have successfully produced papillary necrosis in the experimental animal. Levaditi<sup>23</sup> produced the lesion in rabbits, guinea pigs and mice by subacute poisoning with vinylamin. Rehns<sup>24</sup> produced the lesion in rabbits and guinea pigs, but not mice or rats, by administration of tetrahydroquinoline and its methyl esters. The mode of action of these chemicals, and their relation, if any, to fat metabolism, are unknown to us.

The experimental production of papillary necrosis in rats by a fat-free diet has been detailed earlier in this report. It was shown by Burr and co-workers that the deficiency is chiefly one of unsaturated long chain fatty acids; that a very small amount of these may restore normal fat metabolism; and that although the fat-deficient animals synthesize fat, they cannot synthesize the necessary long chain unsaturated fatty acids. It may be very significant that in diabetics there exists a profound disturbance in fat metabolism, with uncontrolled overproduction of fatty acids. The non-diabetics we have studied were all elderly men with chronic urinary tract obstruction and infection, with anemia and azotemia, all of which were additive in producing debility and malnutrition, with its accompanying disturbance of fat metabolism (e.g., "starvation acidosis"). E. M. Boyd<sup>27</sup> found that during fever neutral fat increases 50 per cent, but total and free cholesterol and phospholipids fall, after an initial rise. He noted that the iodine number of plasma fatty acids fell markedly after an initial rise.

It may be said, then, that disturbed fat metabolism is a common factor in diabetes; in non-diabetics with debility, malnutrition, and sepsis; and in the experimental animal on fat-free diet. It is not possible to say at this time whether a deficiency in unsaturated fatty acids plays a direct rôle in the pathogenesis of papillary necrosis, or whether it plays an indirect rôle by inducing alterations in renal hemodynamics, or in the responses to infection.

Although azotemia is commonly found in patients with this lesion, it cannot be the primary mechanism, for papillary necrosis is not commonly found in diseases that produce uremia most commonly, i.e., arteriolar nephrosclerosis, chronic glomerulonephritis, and chronic progressive pyelonephritis. Uremia and azotemia undoubtedly do play a significant part in the debility and malnutrition of these cases. Further, in diabetics, the illness may be fatal within a far shorter time than is found in uremia. It would seem that azotemia and uremia contribute to the lesion but are not its causes, and rather may be caused by it.

Papillary necrosis is not invariably fatal, for healing does occur, as is demonstrated in our case 8; in a case reported by Edmondson et al.<sup>1</sup>; and in

## BIBLIOGRAPHY

1. EDMONDSON, H. A., MARTIN, H. E., and EVANS, N.: Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus, *Arch. Int. Med.*, 1947 lxxix, 148-175.
2. GÜNTHER, G. W.: Die Papillennekrosen der Niere bei Diabetes, *München. med. Wchnschr.*, 1937, lxxxiv, 1695-1699.
3. ALKEN, C. E.: Die Papillennekrose, *Ztschr. f. Urol.*, 1938, xxxii, 433-438.
4. PELLEGRIN, F. A.: Necrotizing renal papillitis, *Permanente Foundation Med. Bull.*, 1947, v, 66-74.
5. ROBBINS, S. L., MALLORY, G. K., and KINNEY, T. D.: Necrotizing renal papillitis: a form of acute pyelonephritis, *New England Jr. Med.*, 1946, ccxxxv, 885-893.
6. HARRISON, J. H., and BAILEY, O. T.: Significance of necrotizing pyelonephritis in diabetes mellitus, *Jr. Am. Med. Assoc.*, 1942, cxviii, 15-20.
7. BURR, G. O., and BURR, M. M.: New deficiency disease produced by rigid exclusion of fat from diet, *Jr. Biol. Chem.*, 1929, lxxxii, 345-367.
8. BURR, G. O., and BURR, M. M.: On the nature and rôle of fatty acids essential in nutrition, *Jr. Biol. Chem.*, 1930, lxxxvi, 587-621.
9. WESSON, L. G., and BURR, G. O.: Metabolic rate and respiratory quotients of rats on fat-deficient diet, *Jr. Biol. Chem.*, 1931, xci, 525-539.
10. BURR, G. O., BURR, M. M., and BROWN, W. R.: On nutritive value of certain oils, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 905-907.
11. BURR, G. O., BURR, M. M., and MILLER, E. S.: On fatty acids essential in nutrition, *Jr. Biol. Chem.*, 1932, xcvi, 1-9.
12. BURR, G. O., and BROWN, W. R.: On fatty acids essential in nutrition, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1349-1352.
13. HANSEN, A. E., and BURR, G. O.: Studies on iodine absorption of serum in rats fed on fat-free diets, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1200-1201.
14. HANSEN, A. E., and BURR, G. O.: Iodine numbers of serum lipids in rats fed on fat-free diets, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1201-1203.
15. BURR, G. O., and BEBER, A. J.: Metabolism studies with rats suffering from fat deficiency, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxi, 911-912.
16. BURR, G. O., BROWN, J. B., KASS, J. P., and LUNDBERG, W. O.: Comparative curative values of unsaturated fatty acids in fat deficiency, *Proc. Soc. Exper. Biol. and Med.*, 1940, xlv, 242-244.
17. BORLAND, V. G., and JACKSON, C. M.: Effects of fat-free diet on structure of kidney of rats, *Arch. Path.*, 1931, xi, 687-708.
18. DAVSON, J., and LANGLEY, F. A.: Papillitis renis necroticans, *Jr. Path. and Bact.*, 1944, lvi, 327-333.
19. SHEEHAN, H. L.: Medullary necrosis of kidneys, *Lancet*, 1937, ii, 187-189.
20. MENKIN, V.: Biochemical factors in inflammation and diabetes mellitus, *Arch. Path.*, 1942, xxxiv, 182-195.
21. MENKIN, V.: On mechanism of enhanced diabetes with inflammation, *Am. Jr. Physiol.*, 1941, cxxxiv, 517-541.
22. MALLORY, G. K., CRANE, A. R., and EDWARDS, J. E.: Pathology of acute and healed experimental pyelonephritis, *Arch. Path.*, 1940, xxx, 330-347.
23. LEVADITI, C.: Recherches expérimentales sur la nécrose de la papille rénale, *Arch. internat. de pharmacodyn. et de therap.*, 1901, viii, 45-63.
24. REHNS, J.: D'une nécrose typique de la papille rénale déterminée par la tétrahydroquinoléine et certains de ses dérivés, *Arch. internat. de pharmacodyn. et de therap.*, 1901, viii, 199-202.
25. TRUETA, J., et al.: Studies of the renal circulation, 1947, Blackwell, Oxford, Pp. 187.
26. MELLGREN, J., and REDELL, G.: Zur Pathologie und Klinik der Papillitis necroticans renalis, *Acta chir. Scandinav.*, 1941, lxxxiv, 439-457.
27. BOYD, E. M.: Lipopenia of fever, *Canad. Med. Assoc. Jr.*, 1935, xxxii, 500-506.



the portal venous system, since this type of vascular pathology has been found both in the intra- and extrahepatic groups.

The normal venous pressure in the portal system is higher than in the systemic veins because the portal blood after passing through the capillaries of the gastrointestinal tract, spleen and pancreas must traverse another capillary bed, the liver sinusoids, before it enters the inferior vena cava. The normal portal venous pressure has been found to be 10 to 15 cm. of saline. In the presence of portal bed block, either intra- or extrahepatic, the state of so-called portal hypertension develops with pressures varying from 25 to 50 cm. of saline. One of the collateral channels whereby the portal blood returns to the systemic venous system in these conditions is the esophageal veins. These vessels do not anastomose freely with the systemic system so that they frequently become greatly enlarged and varicosed. Hemorrhage from them is a common complication of portal hypertension and carries with it a very high mortality rate. The cause of rupture of these blood vessels has not been satisfactorily explained, but in part it is believed due to the relatively high venous pressure within them. Wangenstein<sup>2</sup> has suggested that it may be due to peptic ulceration of the esophageal mucosa over them, because of the reflux of acid gastric contents into the esophagus.

#### DIAGNOSIS

The diagnosis of bleeding esophageal varices should be considered along with the other causes of esophageal-gastrointestinal bleeding in any patient who gives a history of hematemesis or melena. A sudden massive hematemesis is frequently the first sign that a patient has a portal bed block, especially of the extrahepatic type, since there are few premonitory symptoms of the disease. The diagnosis of a portal bed block with esophageal varices is suggested by such a history, especially if an enlarged spleen is found on physical examination. The blood, as a rule, shows a secondary anemia, a leukopenia and a thrombocytopenia. If the block is intrahepatic the liver may be shrunken, normal or enlarged and in the extrahepatic it is usually normal in size. The two types may be further differentiated by liver function tests. When the block is intrahepatic, there is usually a high retention of bromsulfalein, a reversal of the albumin-globulin ratio with a low level of serum albumin, a positive cephalin flocculation test and an elevated prothrombin time. If the block is extrahepatic all these liver function tests are usually normal. The most important diagnostic procedure, however, in patients suspected of having bleeding esophageal varices is a roentgenologic examination of the esophagus with a thick suspension of barium, as first described by Wolf<sup>3</sup> and later Schatzki<sup>4</sup> (figure 1). The visualization of the blood vessels by this technic depends to a great extent on the skill of the roentgenologist. Direct visualization of the lower end of the esophagus by esophagoscopy is another aid in diagnosis. The demonstration of esophageal

General Hospital over a 12 year period from 1934 to 1945. He found that in the cirrhotic group only 40, or 37 per cent, were alive one year after the diagnosis of esophageal varices was made. In the Banti's syndrome group 18, or 90 per cent, were alive. This higher mortality rate in the patients with cirrhosis is due undoubtedly to the fact that the patients are in an older age group. In addition and of extreme importance is the fact that they for the most part have severely damaged livers, whereas the Banti's group are relatively young and have essentially normal livers. Shull<sup>8</sup> in these same patients found that in the cirrhotic group 90, or 83 per cent, died from all causes. Of extreme significance, however, he found that 41, or 45 per cent, of those that died succumbed to massive esophago-gastrointestinal hemorrhage. In the Banti's group, seven, or 35 per cent, died from all causes and of these five, or 71 per cent of the deaths were due to hemorrhage. The mortality rates from hemorrhage alone in all the patients of the two groups were 38 per cent for the cirrhotics and 25 per cent for the Banti's syndrome group. In addition it is believed that hemorrhage was an important contributing factor in the death of many of the other patients who died from liver failure and other causes. This is especially apt to be true in a group with intrahepatic block, because in many of these patients the serum albumin level is already low due to the liver disease, and as a result of the severe hemorrhage a further rapid reduction takes place. Moreover in the presence of a diseased liver restoration of the serum albumin to a normal level seldom occurs.

The analysis of these cases is of great significance, since it demonstrates the grave prognosis once esophageal varices are diagnosed and the high mortality rate due to hemorrhage from them. At best bleeding esophageal varices cause prolonged disability, since patients after severe hemorrhage frequently require many weeks to months of hospitalization with expensive therapeutic measures. Numerous blood transfusions are essential in many cases to prevent death from shock, and in some cases the blood escapes almost as fast or faster than it can be administered. Under such conditions the bleeding may only be stopped by the placing of a balloon in the stomach which, after inflation, is drawn up against the cardia by means of traction on the rubber tube to which the balloon is attached, as reported by Rowntree et al.<sup>9</sup>

✓ The realization of this high morbidity and mortality due to the bleeding from esophageal varices has spurred us on in an attempt to lower the portal hypertension and reduce the amount of blood in the esophageal varices by formation of various types of portal systemic venous shunts. The treatment of bleeding esophageal varices by various surgical procedures has been attempted for many years. The demonstration by Eck<sup>10</sup> in 1877 that the portal venous blood could be shunted directly into the systemic venous system by anastomosing the portal vein directly to the inferior vena cava in experimental animals, thereby by-passing the liver, stimulated surgeons in the latter part of the 19th century and the early part of the 20th century to perform

tube method, thereby reducing the incidence of thrombosis at the site of the anastomosis. Sixth, there are no vital structures in the left upper quadrant of the abdomen, the region through which the surgical approach is made for this type of shunt, similar to the common bile duct or the hepatic artery which lie in such close proximity to the region where it is necessary to dissect out the portal vein and the inferior vena cava to perform a direct portacaval anastomosis. This last is a point of great practical importance since in either type of shunt operation structures are obscured frequently by bleeding from innumerable small collateral venous channels. An error of a few millimeters in the region of the gastrohepatic ligament in searching for the portal vein may irreparably damage the common bile duct or the hepatic artery with serious consequences, whereas in the splenic area such catastrophes are not as likely to occur since the margin of safety in this region can be measured in centimeters rather than millimeters.

During the past four years at the Massachusetts General Hospital from 1945 to 1948 inclusive, 34 patients with portal hypertension have had various types of portal systemic venous shunts constructed by the suture technic for bleeding esophageal varices. These operative procedures have not been performed on patients unless there was a history of esophago-gastrointestinal bleeding, nor have they been done for the relief of ascites alone. It has been considered advisable in developing this new type of surgery to subject only those patients in whom severe or repeated hemorrhages have taken place in an attempt to see whether future bleedings could be prevented. In this group of patients there were 20 with the intrahepatic type of portal bed block due to cirrhosis of the liver and 14 patients with Banti's syndrome, or congestive splenomegaly, the extrahepatic type of portal bed block. The youngest patient in the group was six years of age and the oldest 65 years. Both had the extrahepatic type of portal bed block, the former presumably of congenital origin due to obliteration of the portal vein and the latter due to thrombosis of the portal venous system of idiopathic origin. The mean age in this group was 36 years. The ages of the intrahepatic group due to cirrhosis of the liver ranged from 27 years to 60 years with a mean age of 44 years. Seven patients in the latter group died as a result of the operative procedure, a mortality rate of 35 per cent. There were no deaths in the Banti's syndrome group, making an operative mortality rate of 21 per cent for the entire group. It is of interest that the operative mortality rate has dropped with the increased experience gained in this type of surgery and the better selection of patients for the procedure, since 20 patients were operated upon in the year 1948 with two deaths, an operative mortality rate of only 10 per cent. Both of them occurred in the cirrhotic group. These statistics indicate, as might be expected, that the risk of this type of surgery which frequently requires four to six hours of anesthesia is greater in those patients with cirrhosis because of the underlying liver disease.

An analysis of the causes of death in these seven patients reveals that four of them died within a few hours of uncontrollable hemorrhage from the

pexy; second, ligation of the coronary vein of the stomach and a second omentopexy; and third, a transthoracic ligation of the peri-esophageal veins.

A direct portacaval shunt, the Eck type of fistula, anastomosing the portal vein to the inferior vena cava was attempted in eight patients. It was possible to perform it in only three of them because in the other five the extreme vascularity in the region of the gastrohepatic ligament prevented exposure of the portal vein. In one patient the common bile duct and gall bladder were injured, necessitating a choledochojejunostomy to reestablish the flow of bile into the intestinal tract and also a cholecystectomy. This patient at a later operation had a splenectomy and a satisfactory end-to-side splenorenal shunt performed. The direct portacaval type of anastomosis was chosen in these eight patients for various reasons. Splenectomy had been previously performed in five of them, which has been found to preclude the construction of a splenorenal shunt at a later date because of thrombosis and secondary fibrosis of the splenic vein. For this reason it was necessary to attempt some other form of shunt in these patients and the direct portal vein to inferior vena cava type of anastomosis was chosen. In two other patients this procedure was selected because the spleen in both was only slightly enlarged, indicating that the splenic vein would not be large enough with which to create a shunt of sufficient size to reduce the portal hypertension. In the remaining patient it was chosen because three other surgeons who had operated upon him had considered a splenectomy to be too formidable a procedure to perform, so that a direct portacaval shunt was attempted almost of necessity. It is of interest that the portal bed block was intrahepatic in three of the patients and extrahepatic in the other five. Two of the patients died; one in whom the shunt was constructed succumbed because of thrombosis of the hepatic artery, the result of operative trauma. In the other one the operation had to be discontinued even before the portal vein was exposed because of uncontrollable bleeding in the operative field and despite numerous transfusions the patient died from postoperative hemorrhage. Both of these patients had the intrahepatic type of portal bed block with severe impairment of liver function from portal cirrhosis, which undoubtedly played some rôle in their deaths.

A successful portacaval anastomosis with survival was performed in only two of the patients, one with intrahepatic block and the other of the extrahepatic type. Both of these patients had had previous splenectomies without relief from massive bleeding. It is at least encouraging that they are alive and have had no further esophago-gastrointestinal hemorrhages for periods of six months in one case and 12 months in the other. The difficulty encountered in attempting to perform a portal vein to inferior vena cava shunt in patients with the so-called Banti's syndrome, the extrahepatic type of portal bed block, who have had previous splenectomies cannot be over-emphasized, as has already been reported,<sup>15</sup> since in four of these previously splenectomized patients it was possible only in one to create a satisfactory shunt.

improved since the postshunt episodes of hemorrhage have not been as severe as the prior ones.

In summary, it can be stated that the construction of various types of portal systemic venous shunts represents a new chapter in the treatment of bleeding esophageal varices, a condition which heretofore has failed to respond to other forms of treatment. In the four year period from 1945 to 1948 inclusive, 34 patients at the Massachusetts General Hospital have been subjected to this type of surgery because of the chief complaint of massive esophago-gastrointestinal hemorrhages. The chief benefit from this type of procedure, that has been observed to date, has been the cessation of bleeding in a majority of patients that have had a satisfactory shunt performed, either a direct portacaval or a splenorenal type. There are 24 patients in this group that can be classified in this category and only one of them has bled since the operation was performed, an incidence of only 4 per cent of bleeding.

The postoperative follow-up studies in reference to liver function at present are incomplete. The bromsulfalein retention test and the serum albumin level in the cirrhotic group of patients reveals little if any improvement in these functions of the liver. In the Banti's syndrome group, they reveal little if any impairment following the construction of the shunt. The cephalin flocculation test in the majority of the cirrhotic patients shows slight improvement from  $4+ - 3+$  to  $3+ - 2+$ . The most striking improvement has been in the level of the hemoglobin, as would be expected, since esophago-gastrointestinal bleeding has ceased in the majority of patients. The pre-operative levels varied from 7.4 to 12.4 grams of hemoglobin per 100 cubic centimeters of blood and the postoperative levels have been maintained at from 11 to 17.5 grams of hemoglobin. The period of postoperative follow-up is of necessity short, but it ranges from four to 34 months. A true evaluation of the procedure necessarily must await a greater lapse of time, but at the present writing the results are definitely encouraging.

### CONCLUSIONS

1. The establishment of portal systemic venous shunts represents a new and encouraging chapter in the treatment of bleeding esophageal varices secondary to portal hypertension.
2. Splenectomy and the suture type of end-to-side splenorenal anastomosis with preservation of the kidney is recommended as the most satisfactory operative procedure.
3. It is believed that a surgeon should not do a splenectomy in a case of portal hypertension unless he is prepared to do a splenorenal anastomosis at the same operation, since this may be the only opportunity to construct a satisfactory portal systemic venous shunt.
4. The postoperative studies over periods of 4 to 34 months in patients in whom satisfactory portal systemic venous shunts have been performed

# PHARMACODYNAMICS OF PULMONARY ABSORPTION IN MAN. II. THE INFLUENCE OF VARIOUS DILUENTS ON AEROSOL AND INTRATRACHEAL PENICILLIN \*

By JOHN F. BEAKEY, EDWARD A. GAENSLER and MAURICE S. SEGAL, F.A.C.P., *Boston, Massachusetts*

THE pharmacodynamics of pulmonary absorption has not been generally considered in the clinical reports on the success of aerosol and intratracheal therapy. There is equally meager information regarding the action of various pharmacologically active diluents in promoting or retarding absorption of penicillin from the pulmonary epithelium.

In a recent study<sup>1</sup> we described various factors influencing absorption from the normal human lung. Crystalline penicillin G potassium (100,000 units) in physiologic saline was administered intramuscularly, intratracheally and by oxygen-aerosolization. The blood levels and urinary excretion, following intratracheal injection, were lower but more sustained than those following intramuscular administration. Rapid absorption would normally be expected from such a large and vascular area as the alveolar bed. The lung was thus demonstrated as a reservoir capable of considerably retarding the expected rate of absorption. By comparing the total urinary excretion of the intratracheal with aerosol method of administration, the amount of penicillin actually reaching the lung by the latter route was calculated to be about 35 per cent. Easily determinable wastage, occurring during aerosolization, accounted for some of the loss.

Although physiologic saline has been most generally used as the diluent or vehicle for penicillin aerosolization, other diluents, which are active substances themselves, have been suggested. Inhalation of 0.5 to 1 per cent adrenalin has been notably effective in relieving bronchospasm in the asthmatic,<sup>2,3</sup> neosynephrin is a potent bronchovasoconstrictor which shrinks mucous membranes rapidly. Combination of either or both of these two solutions with penicillin was a natural development when the need arose for such medication in addition to penicillin itself. While such vehicles have been used with penicillin, others suggest themselves as effective diluents because of their inherent pharmacological activity. The search for diluents which might either enhance or supplement the action of penicillin or act independently to advantage has attracted relatively few investigators.

\* Received for publication September 11, 1948.

From the Department of Inhalational Therapy, Boston City Hospital and the Department of Medicine, Tufts College Medical School.

This study was aided by a grant from the Commercial Solvents Corporation.

tion occurring with their use must be attributed to a local chemical or mechanical action.

# RESULTS

For an analysis of data in terms of therapeutic effectiveness, the bactericidal activity *in vitro* must be correlated *with* clinical or *in vivo* results. The average minimal effective level at which most gram-positive pathogens are killed faster than they multiply, or the concentrations at which these organisms fail to grow in culture, is 0.04 (0.039) unit of penicillin per c.c. of serum. For purposes of analysis, therefore, we elected to call this the "minimum therapeutic level." This, and higher levels, we have called "positive"; levels less than 0.04 unit per c.c. of serum we have called "negative."

Following aerosolization of penicillin in each diluent, serum levels were evaluated according to the above criteria. The overall effectiveness of a diluent was judged by the following determinations. First, by the number of sera at or exceeding 0.04 unit per c.c. throughout the entire two hours;

CHART I

Diluent	Physiologic Saline	Neosynephrin (1%)	Epinephrine (1%)	Triethylene Glycol (100%)	Chlorophyll (100%)	Pantopaque (100%)
No. of sera tested	36	35	33	33	27	26
Total percentage of positive sera*	69	66	33	18	44	11
Percentage of sera still positive at the end of two hours	25	45	9	9	0	11
Percentage of sera exceeding minimum therapeutic level	39	29	9	9	22	0

\* 0.04 unit or more.

this is expressed as the *total percentage of positive sera* for each vehicle. Second, by the ability of any particular diluent to affect absorption so that blood levels are positive for a longer period of time; this is reflected in the *percentage of sera still positive at the end of two hours*. Third, by the *percentage of sera whose penicillin activity exceeds the minimum therapeutic level* (i.e. more than 0.04 unit per c.c. of serum). Determination of the latter is important since the "minimum therapeutic level" is insufficient for complete bactericidal activity against many strains of susceptible organisms. Diluents which will so affect absorption that levels in a higher range result, must, therefore, be considered particularly effective. A summary of each aerosolized diluent analyzed according to these criteria is given in chart 1. Neosynephrin is a potent bronchovasoconstrictor with poor bronchodilator properties; epinephrine has less vasoconstrictor properties but is a

powerful bronchodilator. One per cent neosynephrin and 2.5 per cent racemic epinephrine (Vaponefrin, analogous to 1.5 per cent U.S.P. epinephrine) were used as diluents. The effects on absorption of these two drugs as contrasted to saline were reflected in the blood levels (chart 2 and figure 1).

The total percentage of positive sera with saline (69 per cent) and neosynephrin (66 per cent) are essentially the same; whereas, only 33 per cent

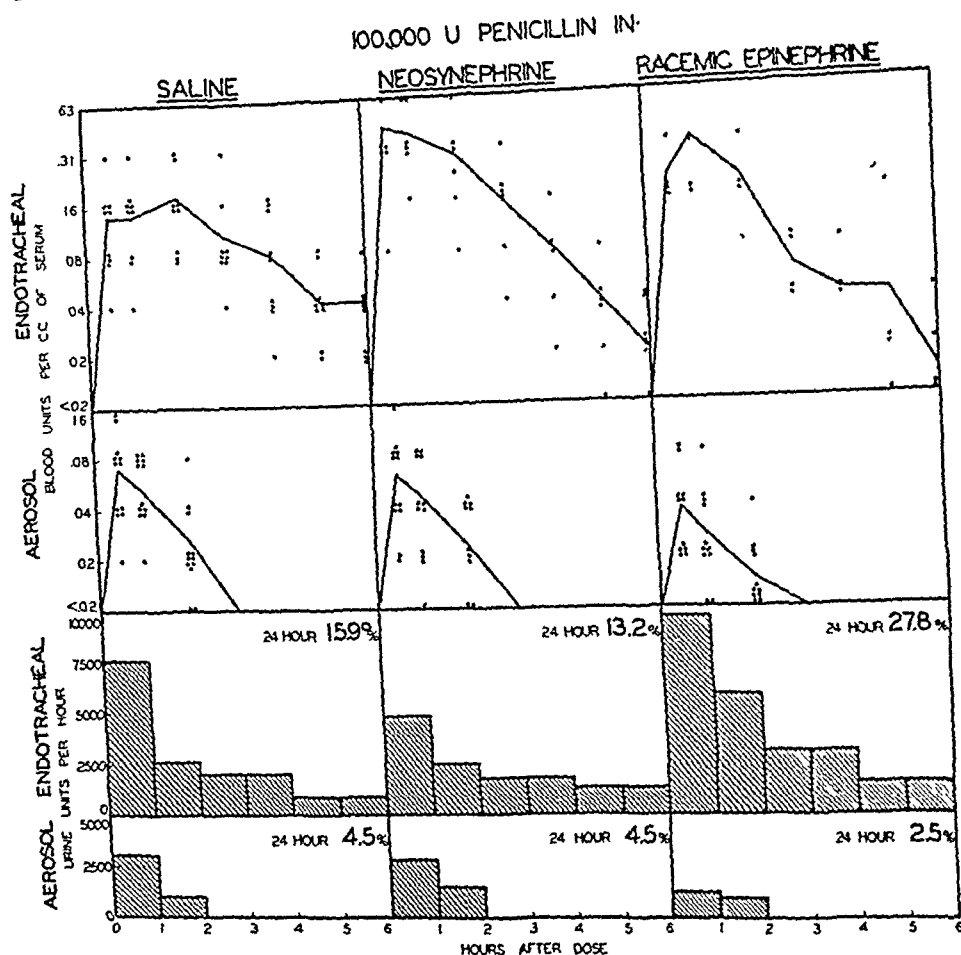


FIG. 1. Blood level curves and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by intratracheal and aerosol routes of administration in various diluents.

positive sera were obtained with racemic epinephrine (chart 1). The differences in the percentage of sera still positive at the end of two hours demonstrate the vasoconstricting action of neosynephrin on the absorption of penicillin; 45 per cent of the two-hour sera were positive as compared to 25 per cent with saline and only 9 per cent with epinephrine. The percentage of sera exceeding the minimum therapeutic level follows much the same pattern: with saline, 39 per cent, with neosynephrin, 29 per cent; and with epinephrine, 9 per cent. Total urinary excretions were consistent with the blood



priate for intrapulmonary use. Since triethylene glycol and Pantopaque are relatively viscid and not easily aerosolized by the conventional nebulizer, a special Vaponefrin nebulizer, dispensing a larger particle size, was used.

These diluents, whose effect on absorption and excretion of penicillin is of a chemical or mechanical action, have a marked effect on the serum levels (chart 2 and figure 2). The blood levels and total urinary excretion were consistently lower than those obtained with physiologic saline. The *total percentage of positive sera* (chart 1) using triethylene glycol (18 per cent) or Pantopaque (11 per cent) compare unfavorably with that of saline (69 per cent); chlorophyll produced a somewhat higher number of sera in the therapeutic range (44 per cent). The *percentage of sera positive at the end of two hours* and the *percentage of sera whose penicillin activity exceeded the minimum therapeutic level* also did not compare favorably to that of saline when these diluents were used.

#### INTRATRACHEAL ADMINISTRATION

Direct instillation into the trachea should yield accurate data on the manner in which diluents affect absorption of penicillin from the tracheo-bronchial tree. With aerosolization, losses occur at the apparatus, into the air and in the mouth. We have shown elsewhere that only 35 per cent of an aerosolized substance actually reaches the lung. Exact quantitative evaluation is therefore difficult. In contrast, no losses occur with intratracheal administration unless the injected substance causes enough chemical irritation to produce cough and expectoration in spite of topical anesthesia.

We, therefore, elected to inject directly into the trachea the same diluents previously used by the aerosol route. Penicillin assay of bloods and urines following this type of administration were tabulated (chart 3) and correlated with the aerosol data (figures 1 and 2).

The results following the use of neosynephrin, epinephrine and saline as penicillin vehicles, by both aerosol and intratracheal routes, are compared in figure 1. Neosynephrin 1:100 was used for aerosolization but was diluted to 1:1,000 for intratracheal injection; racemic epinephrine (analogous to 1.5 per cent U.S.P. epinephrine) was employed for inhalation; and epinephrine for direct instillation was diluted to a 1:10,000 concentration because marked side reactions occurred with higher concentrations. Despite such low dilutions, these substances exerted a profound effect on the blood levels and urinary excretion of penicillin when injected endotracheally.

Certain striking facts are partially obscured by the logarithmic ordinates of our graphs. Actually, the average blood level at one-half hour following neosynephrin (0.43 unit) was exactly three times that obtained when saline was the diluent (0.14 unit). The ratio was maintained fairly closely at one hour and less so at two hours; at four hours, the average levels were the same (0.08 unit). The neosynephrin curve remained within the therapeutic range for five hours; the saline curve remained so for six hours. The

CHART III—Continued

	Blood							Urinary Excretion					
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.	Total
Pantopaque													
P. M.	.63	.31	.08	.16	.08	.04	.02	33,250	8,500	17,500	15,375	89	74,714
P. F.	.31	.31	.08	.04	.03	.02	.01	27,000	10,500	16,500	402	200	54,602
A. H.	.16	.08	.04	.02	—	0	0	—	—	—	—	—	—
J. F.	.31	.16	.08	.04	.02	0	0	33,750	5,000	8,375	2,122	162	49,409
J. O'D.	.31	.31	.08	.08	.03	0	0	12,500	4,992	6,718	800	200	25,210
Average	.34	.23	.07	.07	.04	.01	.01	26,625	7,248	12,273	4,675	162	50,983
Human Serum													
J. C.	.23	.08	.08	.04	.02	0	0	4,000	4,000	2,500	2,500	115	12,115
R. C.	.16	.16	.16	.08	.02	.02	0	6,240	6,240	12,500	12,500	438	37,918
R. W.	.16	.08	.08	.06	.06	.04	.04	12,500	12,500	12,500	6,240	1,575	45,315
J. H.	.31	.63	.31	.31	.16	.08	.04	18,740	25,000	12,500	1,560	2,850	60,650
Average	.22	.24	.16	.12	.07	.04	.02	10,370	11,935	10,000	5,700	1,245	39,250

penicillin blood curve with endotracheal epinephrine lay between the neosynephrin and saline curves and remained within the therapeutic range for five hours.

The amount of penicillin excreted in the urine following endotracheal administration with these diluents varied. Average recovery in the urine after the use of epinephrine was greater at each time interval than with either neosynephrin or saline and the total average excretion was approximately twice that obtained with either of the other vehicles. Although the total average excretion with neosynephrin was slightly lower than with saline, most of this difference occurred in the first hour; after the fourth hour, recovery with neosynephrine was moderately higher than with saline.

The blood level curves following aerosolization of penicillin in each of these diluents have been fully discussed above. Correlation with the endotracheal data just presented discloses fair consistency. However, the lower recovery in the urine following aerosolization with epinephrine is inconsistent with the comparatively high recovery following intratracheal injection with this same substance.

The absorption and excretion of penicillin when injected endotracheally with triethylene glycol, chlorophyll or Pantopaque is compared to saline (figure 2). A micronized crystalline penicillin G potassium powder with an average particle size of less than two micra was mixed with Pantopaque when this substance was studied intratracheally. Unlike all other substances which we injected into the trachea, chlorophyll and especially triethylene glycol were markedly irritating in 100 per cent concentrations and varying amounts of penicillin were lost because of resultant cough and expectoration. It is noteworthy that instillation of Pantopaque did not lead to cough.

bination with penicillin when the clinical picture warranted the use of either to combat bronchospasm, mucosal swelling or both. On the contrary, definite beneficial local effects, in addition to their pharmacologic actions, appeared to be exerted.

Triethylene glycol did not seem to hold any particular advantage as a diluent by either the aerosol or intratracheal routes. As it was too viscid for easy aerosolization with the conventional nebulizer, the blood levels following its administration with a special large particle size nebulizer were disappointing. Moreover, by intratracheal route, it was extremely irritating to the tracheobronchial tree. Low blood levels and urinary excretion may be argued as indicating local retention in the lung; in fact, studies in which triethylene glycol was tagged with radioactive substances indicated a greater local retention of penicillin when combined with this diluent than with other substances.<sup>17</sup> A slowing of absorption would, of course, result in low early blood levels but, conversely, blood samples at later intervals would continue to show penicillin activity, albeit still in the lower ranges. Following intratracheal injection, all individual six-hour levels and one-half of the five-hour levels were zero. Following aerosolization, only one of the 11 sera tested at the end of two hours was within a therapeutic range. With neither route, therefore, could delayed absorption be ascribed to a glycol-penicillin combination. Other reports have described the glycols as enhancing the bactericidal action of penicillin when combined with the latter. In fact, a bactericidal action of glycol alone in the blood stream has been claimed.<sup>18</sup> However, these conclusions were based on a bacteriological technic which used *B. subtilis* as a test organism; normal blood has been shown to exhibit antibodies in various titers for these organisms.<sup>19</sup> A false impression of bactericidal activity in the serum may, therefore, result when *B. subtilis* is used as the test organism. In addition to our routine studies, we repeated the above mentioned study<sup>18</sup> where 100,000 units of penicillin was aerosolized in a mixture of 19 c.c. of triethylene glycol and 1 c.c. of glycerol. We employed the O.E.M. head-tent. A double assay of several blood and urine specimens was done using both streptococcus No. 98 and *B. subtilis* as test organisms. As we could not demonstrate any penicillin in either the blood or urine, we were, therefore, unable to detect either delay in absorption or potentiation of the bactericidal action of penicillin when it was combined with glycol.

Initial blood levels, with chlorophyll as a diluent, were higher than the saline levels, especially when administered intratracheally. With both routes, however, levels were not maintained within a therapeutic range for as long a time as with saline. Chlorophyll, in 25 per cent dilution, was not irritating to the tracheobronchial tree but full strength solution, when given intratracheally, did cause cough despite topical anesthesia. However, chlorophyll may be of practical value when the bacterial flora includes anaerobic organisms. Because it causes more rapid absorption of penicillin, its administration would have to be repeated at shorter time intervals.

2. Both neosynephrin and epinephrine, constrictors of the bronchial mucous membrane, caused higher initial blood levels than corresponding results with saline when injected intratracheally. Levels were sustained within a therapeutic range for five hours. The bronchovasoconstricting action of neosynephrin was more in evidence when aerosolized with penicillin.

3. When the aerosolization of either or both of these substances with penicillin was indicated clinically, their local pharmacologic action on the tracheobronchial tree favorably affected absorption of penicillin. Irritation or side reactions were not present with either route of administration.

4. Triethylene glycol was too viscid for easy aerosolization and too irritating, at full strength, for intratracheal injection. Neither a bactericidal action of its own, enhancement of penicillin activity in the serum nor a delaying action on the absorption of penicillin could be demonstrated.

5. Chlorophyll caused more rapid absorption of penicillin but levels were not maintained within a therapeutic range for as great a length of time as with saline. One hundred per cent solution was irritating to the tracheobronchial tree, but a 25 per cent solution was well tolerated by intratracheal instillation. Chlorophyll with penicillin, in the treatment of mixed gram positive and negative bacterial flora, should be repeated frequently in order to maintain high local antibiotic activity. Chlorophyll (endotracheal) should be of definite value for the management of anaerobic bacterial bronchopulmonary infections.

6. Intratracheal injection of emulsions of penicillin in the lighter iodized oils in the treatment of bronchopulmonary suppurative disease is discussed. The cleansing action of the oil at the site of localized collections of pus and the displacement or "floating" of mucous plugs would permit more effective local action of penicillin injected at the same time.

7. Human serum as a vehicle did not greatly alter the absorption of penicillin from the lung.

#### BIBLIOGRAPHY

1. GAENSLER, E. A., BEAKEY, J. F., and SEGAL, M. S.: Pharmacodynamics of pulmonary absorption in man. I. Aerosol and intratracheal penicillin, *Ann. Int. Med.*, 1949, xxxi, 582.
2. GRAESER, J. B., and ROWE, A. H.: Inhalation of epinephrine for the relief of asthmatic symptoms, *Jr. Allergy*, 1935, vi, 415.
3. SEGAL, M. S., and BEAKEY, J. F.: The use of 1-(3'-4'-dihydroxyphenyl)-2-isopropylamino-ethanol for the management of bronchial asthma. A preliminary report, *Bull. New England Med. Center*, 1947, ix, 62.
4. RAMMELKAMP, C. H.: A method of determining the concentration of penicillin in body fluids and exudates, *Proc. Soc. Exper. Biol. and Med.*, 1942, li, 95.
5. MEAKINS, J. C., SMITH, F., and GOLD, M. A.: A comparative study of some commercial preparations of oral penicillin, *Canad. Med. Assoc. Jr.*, 1946, lv, 97.
6. GOODMAN, L., and GILMAN, A.: *The pharmacological basis of therapeutics*, 1941, pg. 405, Macmillan Co., New York.
7. HARRIS, T. N., and STOKES, J., JR.: Summary of a three year study of the clinical application of the disinfection of air by glycol vapors, *Am. Jr. Med. Sci.*, 1945, ccix, 152.

# TREATMENT OF HEART AND KIDNEY DISEASE AND OF HYPERTENSIVE AND ARTERIO- SCLEROTIC VASCULAR DISEASE WITH THE RICE DIET \*

By WALTER KEMPNER, M.D., *Durham, N. C.*†

THE treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet is either ineffective or dangerous, unless it is done under rigidly controlled conditions. Ineffective, because small or "minimal" additions to the diet may spoil the entire therapeutic result; dangerous, because a strict observance of the diet may lead to a deficiency of vitally important elements unless care is taken that the equilibrium between intake and loss of these substances is maintained. For both reasons, therefore, continuous supervision, over a long period of time, including constant checks of blood and urine chemistry, is essential.

Rigidly controlled conditions are likewise indispensable for the evaluation of the therapeutic results. Claims of positive or negative results based on nothing but blood pressure readings for four to eight weeks before and after treatment and not substantiated by heart films, electrocardiograms, eye-ground photographs and chemical findings do not contribute much to the solution of this problem.

The same authors who a few years ago insisted that the restriction of salt, protein or fat is unwarranted in the treatment of hypertensive and arteriosclerotic vascular disease, now admit the importance of these dietary restrictions. No matter what the value of the restriction of sodium or of chloride or of protein or of cholesterol may be, the fact is: The rice diet contains less sodium and less chloride than any other diet which has been devised to reduce the sodium and chloride intake. It contains less protein than any other diet which has been devised to reduce the protein intake. It contains less cholesterol and other fat than any other diet which has been devised to reduce the cholesterol and fat intake.

The rice diet contains in 2,000 calories less than 5 gm. of fat and about 20 gm. of protein derived from rice and fruit and less than 200 mg. of chloride and 150 mg. of sodium. This does not mean that the patient's caloric intake is restricted to 2,000 calories; it varies according to whether weight gain or weight loss, protein increase or protein decrease is desirable in the individual patient.

\*Read at the Thirtieth Annual Session, American College of Physicians, New York, N. Y., March 30, 1949.

From the Department of Medicine, Duke University School of Medicine.

† This work was supported by grants from the A. H. Hanes Research Fund, the Life Insurance Medical Research Fund, and the U. S. Public Health Service.

and urine shows that the nitrogen equilibrium on the rice diet can easily be maintained (table 1).

There are other indications that, because of the protein sparing action of the carbohydrates, the protein part of the rice diet is adequate and that there is no lack of essential amino acids; e.g., the fact that the production of hemoglobin is normal and that anemia does not develop. Also the fact that blood urea and non-protein nitrogen decrease on the rice diet whereas in starvation and in protein deficiency the body uses its own protein and the non-protein nitrogen and the urea nitrogen in the blood increase.

Other differences between starvation and the rice diet are: in starvation, the serum calcium is decreased, on the rice diet unchanged. In starvation, the plasma protein and the A/G ratio are decreased, on the rice diet unchanged or, if low before, often become normal. In starvation, the blood sugar is decreased, on the rice diet unchanged. In starvation, the carbohydrate tolerance is decreased, on the rice diet increased. In starvation, the serum phospholipids are increased, on the rice diet decreased. In starvation, the CO<sub>2</sub> combining power is decreased, on the rice diet increased. In star-

TABLE I  
Nitrogen Balance After 60 Days on Rice Diet, gm.N in 24 hrs.  
(Averages of 4 consecutive days)

	Intake	Output		Balance
		urine	stool	
W. C. m., 59	4.66	2.61	1.81	+0.24
		4.42		

vation, the blood volume remains unchanged or—in relation to body weight—increases; on the rice diet, according to Murphy's determinations, it decreases. In starvation, the interstitial fluid remains unchanged or increases; on the rice diet it decreases. (N. B., there is no simple relationship between volume changes and clinical course.) In starvation, the excretion of total creatine bodies in the urine is unchanged; on the rice diet it is decreased. In starvation, the excretion of creatine, ammonia and organic acids is increased, on the rice diet decreased. In starvation, the excretion of total sulfate and inorganic phosphate is decreased, on the rice diet markedly decreased (table 2).

In 490 patients with hypertensive vascular disease and an initial non-protein nitrogen of 20 to 45 mg. per 100 c.c. of blood, there was an average decrease of the non-protein nitrogen from 33 to 28 mg. per 100 c.c. of blood after an average period of 98 days. There was an average decrease of the urea nitrogen from 14 to 8 mg. (table 3). These figures are also interesting in another connection: a decreased salt intake in the diet with ensuing hypochloremia is usually followed by an increase in the blood urea nitrogen,

various proteins. It is of no advantage to the patient to receive a large amount of protein with a low biological value which cannot be properly utilized. Moreover, certain patients should use protein only for essential purposes and not merely to supply calories which can just as well be supplied by the oxidation and fermentation of carbohydrates.

The same considerations which apply to protein and essential amino acids are also valid with regard to fat and essential fatty acids. The absolute fat content of rice for instance is small, but the proportion of linoleic acid, an essential fatty acid, is high.

One of the lipids which is supposed to have an important rôle in the development of vascular disease is cholesterol. A high cholesterol concentration in the serum is frequently found in arteriosclerosis, coronary artery disease, exudative vascular retinopathy, hypertensive vascular disease, as well as in diseases of the lens and vitreous body, in uncontrolled diabetes mellitus and in the nephrotic stage of nephritis.

TABLE IV  
Total Serum Cholesterol of 511 Patients with Hypertensive Vascular Disease

	Before	After	Average Period of Rice Diet (Days)
	Rice Diet		
148 Patients with initial concentration below 220 mg. per 100 c.c. serum	186	171	120
363 Patients with initial concentration above 219 mg. per 100 c.c. serum	279	205	102

An easy way to produce arteriosclerosis is by feeding cholesterol to rabbits. In dogs it is not so easy. The aging process in the human species seems to be a change from the dog state to the rabbit state. The cholesterol metabolism becomes inadequate and the average serum cholesterol concentration of men of 50 is higher than that of men of 20 who have an identical cholesterol intake. However, if a 20 year old man has a disease which causes a hypercholesterolemia, the same sequelae may occur as in the 50 year old man. The literature describes cases of arteriosclerosis in diabetic children as young as one year.

We have examined the effect of the rice diet on the total serum cholesterol of 511 patients with hypertensive vascular disease (table 4). In 148 patients (29 per cent) who started the rice diet with a normal serum cholesterol, the average decrease was 15 mg. per 100 c.c. of serum after an average period of 120 days. In 363 patients (71 per cent) who had a hypercholesterolemia before the rice diet, the average decrease was 74 mg. after an average period of 102 days.

These figures show that, no matter from what fatty or non-fatty substances the cholesterol in the body is derived, and by what mechanism a high

TABLE VI

Lipid Phosphorus in Serum of 42 Patients with Hypertensive Vascular Disease  
(Mg. lipid P in 100 c.c. serum)

Before	After 78 Days (Average) on
Rice Diet.	
9.91	8.87

ACIDS AND BASES IN URINE  
*NORMAL*

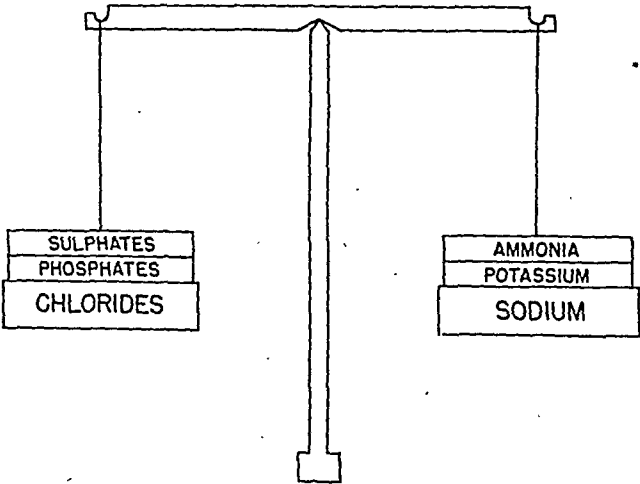


FIG. 3.

ACIDS AND BASES IN URINE  
*RENAL INSUFFICIENCY*

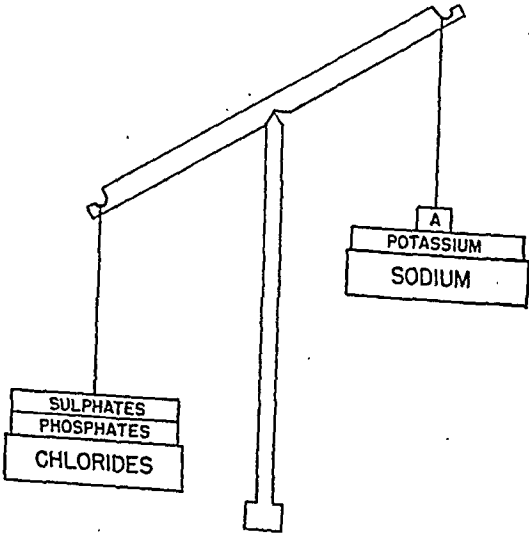


FIG. 4.



Now let me turn from the chemical changes to the clinical changes produced by the rice diet. I will avoid long-winded statistics as much as possible and will try to discuss the main problems by showing you some typical cases as examples of what can be achieved in the individual patient.

The first case is that of a 13 year old school girl in the nephrotic stage of chronic nephritis. It is an example of the disappearance of marked generalized *renal* edema and hypoproteinemia on the rice diet. Early in Jan-

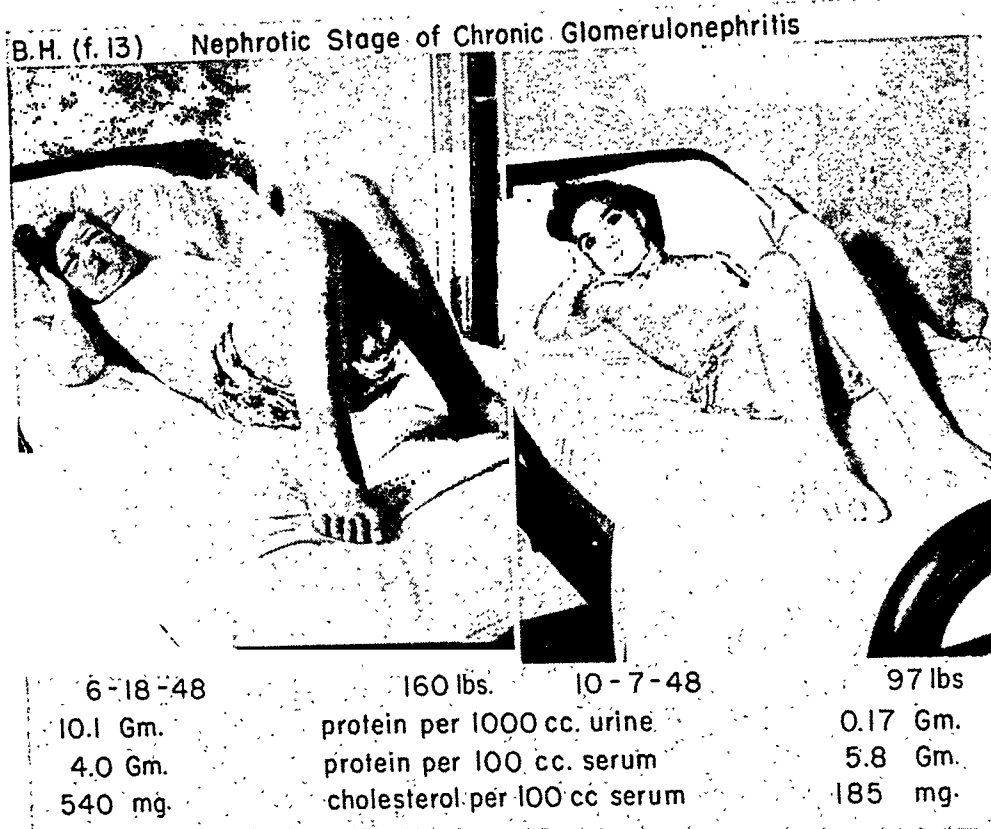


FIG. 6.

uary, 1948, this girl developed swelling of the lower extremities after a sore throat. She was treated by bed rest, salt-poor diet (for part of the time, high protein diet), and penicillin. In February, 1948, massive anasarca developed; a paracentesis was done which resulted in a weight loss of 22 pounds. Later, because of marked dyspnea, a thoracocentesis was necessary and one quart of fluid was removed from the right pleural cavity. During June, the facial edema which had been present since January became worse and the general edema and ascites increased. When the oliguria became serious, the patient was referred to us. The rice diet was started on June 18, 1948. No further paracentesis or thoracocentesis was done. The albuminuria decreased from 10.1 gm. per liter (average during the first 20 days on the rice diet) to 0.17 gm. (average after 111 to 131 days of rice diet). The

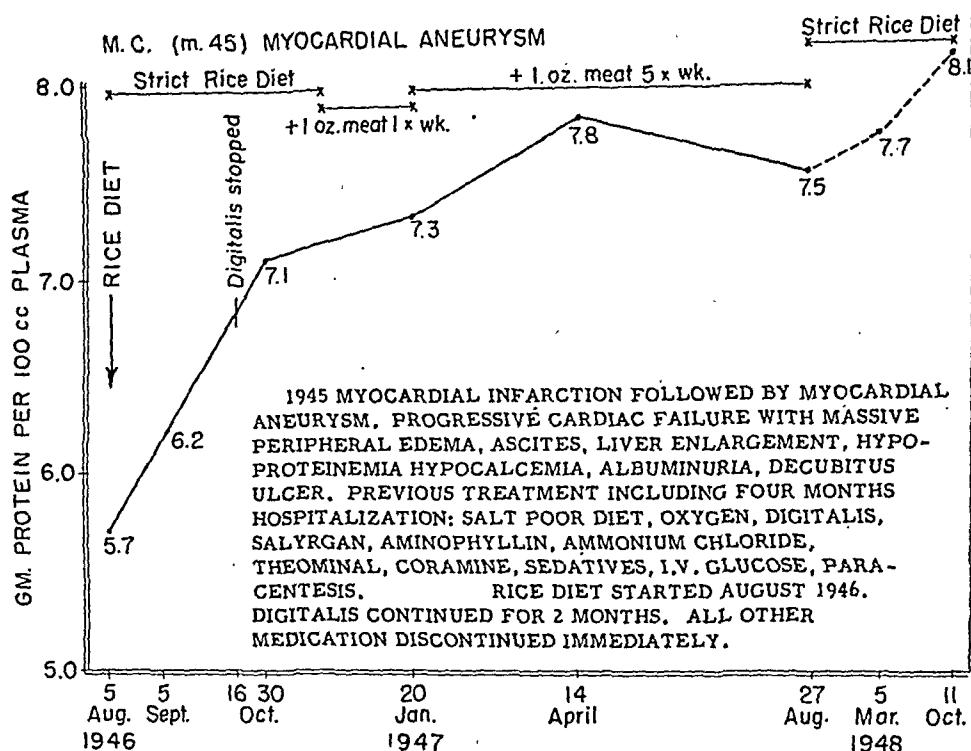


FIG. 8.

plasma protein increased from 4.0 gm. to 5.8 gm. The cholesterol decreased during this period from 540 mg. per 100 c.c. of serum to 185 mg. There was a total weight loss of 63 pounds in 15 weeks with gradual disappearance of ascites and pleural effusion. After eight months on the rice diet, the

M.C. (m. 45)

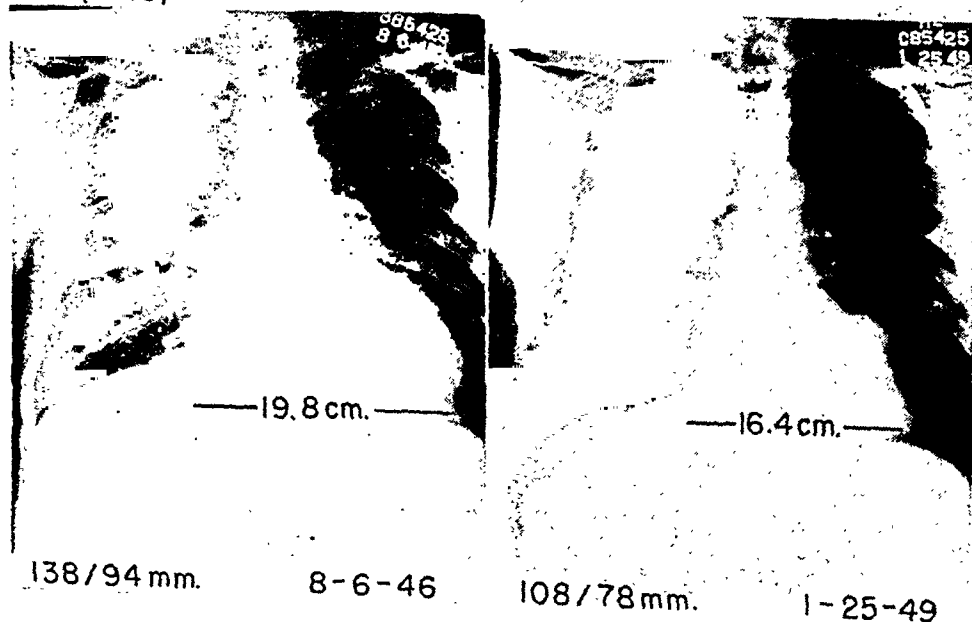


FIG. 9.

was followed by a myocardial aneurysm, progressive cardiac failure with massive peripheral edema, ascites, liver enlargement, hypoproteinemia, hypocalcemia, albuminuria, and decubitus ulcers. Previous treatment, including four months' hospitalization, consisted of salt-free diet, oxygen, digitalis, salyrgan, aminophyllin, ammonium chloride, theominal, coramine, sedatives; i.v. glucose; paracentesis. The rice diet was started August 7, 1946, and was strictly followed; a paracentesis was done August 13. Digitalis was continued for two months, but all other medications were discontinued immediately. There was a loss of weight (edema) of 50 pounds in 10 weeks. Up to the present time (two and one-half years later), the patient has received no medication; he is up and around and completely asymptomatic. The plasma proteins have increased from 5.7 gm. per 100 c.c. to 8.2 gm.

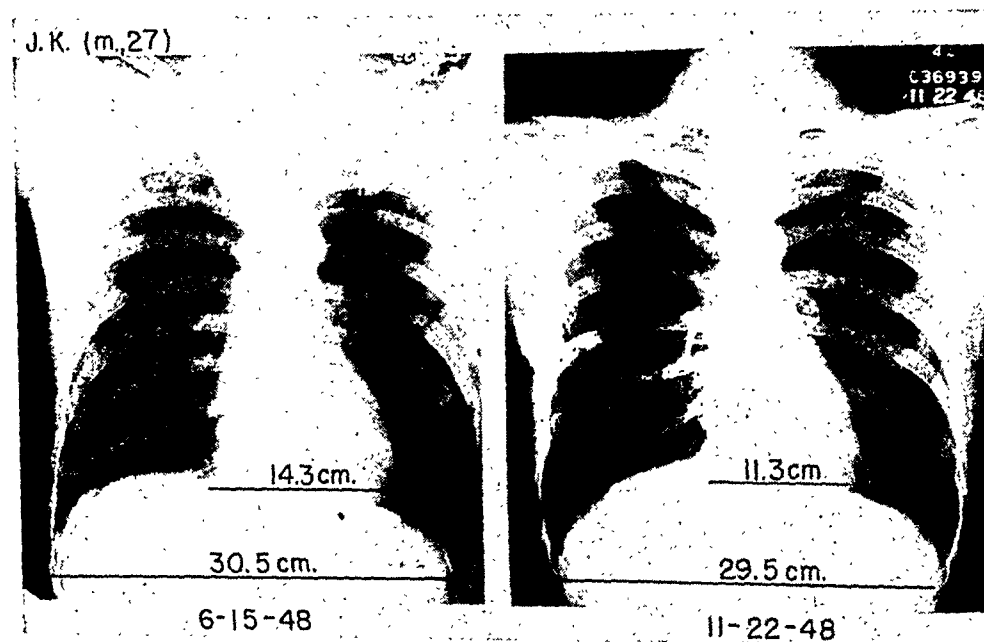


FIG. 11.

The heart is considerably smaller and the aneurysm of the posterior lateral wall of the left ventricle is now clearly visible in the A-P view (figure 9).

The patient, whose eyeground photographs and chest films are shown in figures 10 and 11, is an example of the effect of the rice diet on retinopathy and cardiac enlargement in chronic glomerulonephritis.

The patient was a 27 year old man who two years before admission to Duke Hospital, while in the Navy, had scarlet fever and acute glomerulonephritis, followed by chronic glomerulonephritis. He had been hospitalized for 16 months and treated with rest and various diets. During the month prior to admission, the patient had an exacerbation of his headache; noted blurring of vision and had a generalized convulsion, for which magnesium sulfate was given. At the start of the rice diet the blood pressure was 180

regained his eyesight; papilledema, hemorrhages and most of the exudates had disappeared; the heart had decreased in size with a change in the transverse diameter of 27 per cent.

I have shown you some effects of the rice diet on edema, ascites, heart enlargement and retinopathy in patients with primary kidney disease. I will show you now some characteristic examples of the effect of the rice diet on hypertensive vascular disease without evidence of any primary renal disease. In more than 70 per cent of 777 patients most of whom were seriously ill and had failed to respond to other forms of treatment, the rice diet, given for periods of four to 1,150 days (average 92 days), has proved beneficial; that means that it has produced one or more of the following effects: decrease in the sum of systolic and diastolic blood pressure of at least

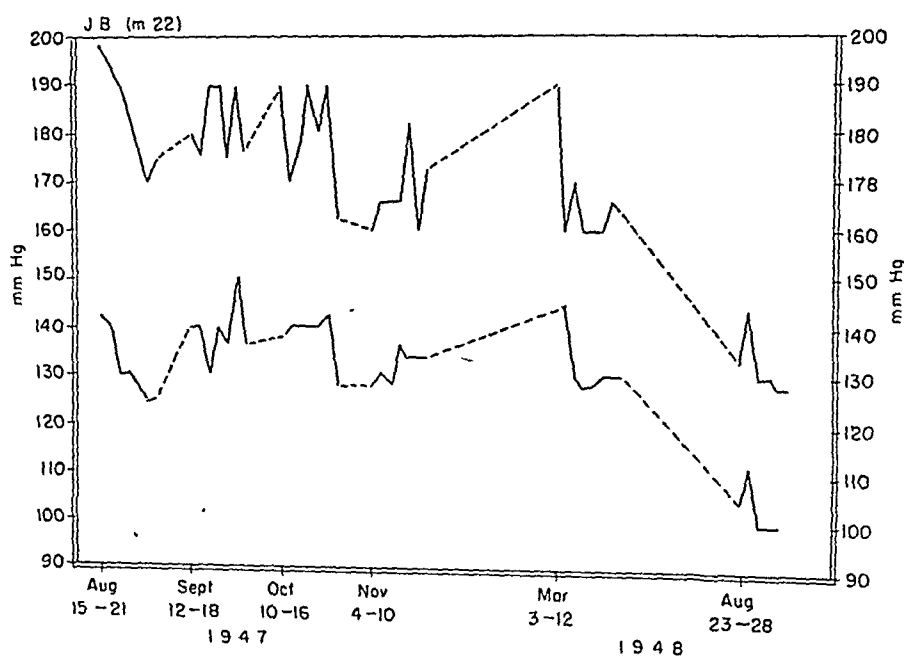
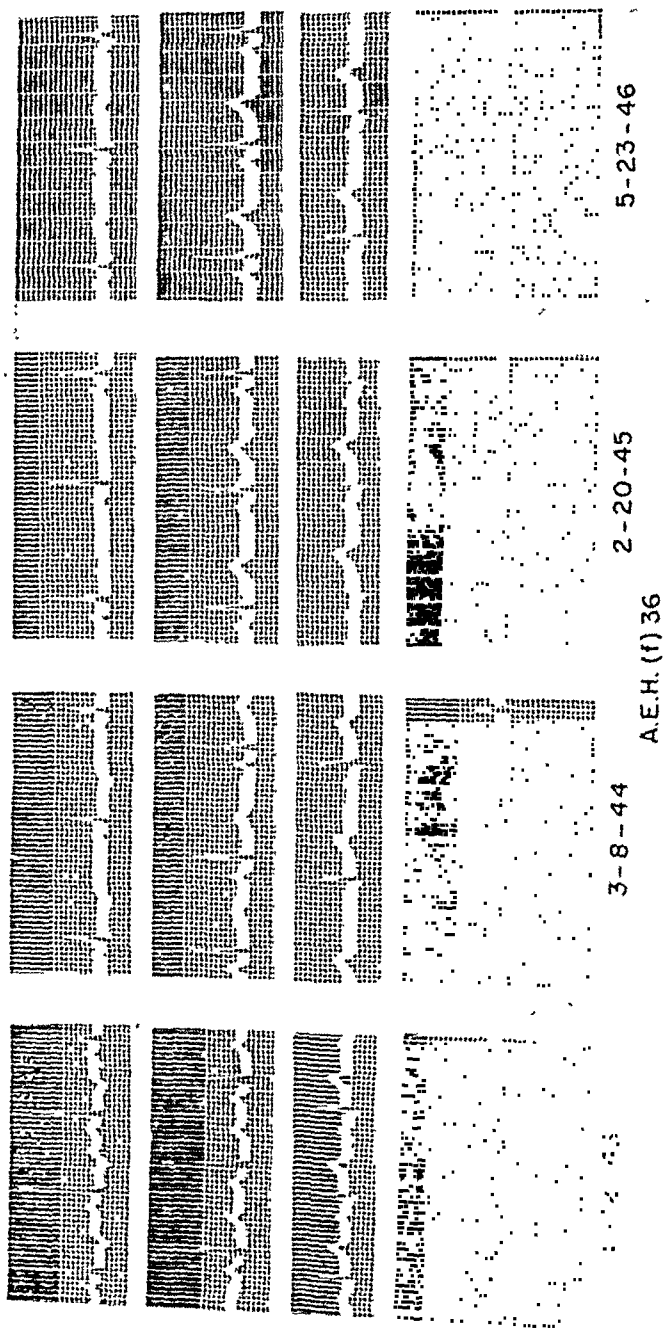


FIG. 13.

40 mm. Hg; reduction in heart size with change in the transverse diameter of 18 per cent or more; change in  $T_1$  from completely inverted to upright; disappearance of severe retinopathy.

I will begin with three typical cases of so-called benign essential hypertension without serious cardiac, renal or retinal complications.

The first one is an example of a satisfactory response to the diet in about four months. It is the case of a 35 year old woman who had had hypertensive vascular disease for 11 years. There was no evidence of any renal excretory involvement. Of two brothers with hypertensive vascular disease, one had died of a stroke at the age of 37. For years, the patient did not feel up to par with increasing fatigue and exhaustion. There was a sensation of pressure and throbbing in the back of the head and in the eyes. From January to April, 1947, because of the appearance of retinal hemor-



Reprinted from the *American Journal of Medicine*, 4, April, 1948.

FIG. 15.

diet, the importance of the time factor becomes obvious: In 392 patients who followed the diet for four to 74 days (average 37 days), there was a definite lowering of the blood pressure in 62 per cent. In 385 patients who followed the diet for 75 to 1,150 days (average 149 days), there was a definite lowering of the blood pressure level in 81 per cent.

The third case with benign essential hypertension is an example of a satisfactory response to the diet in one month. It is the case of a man now 47 years old who was well until he was 37. In March, 1940, he was seen in the New York Hospital. The blood pressure was 165 to 200 systolic and 105 to 135 diastolic. A diagnosis of hypertensive vascular disease was

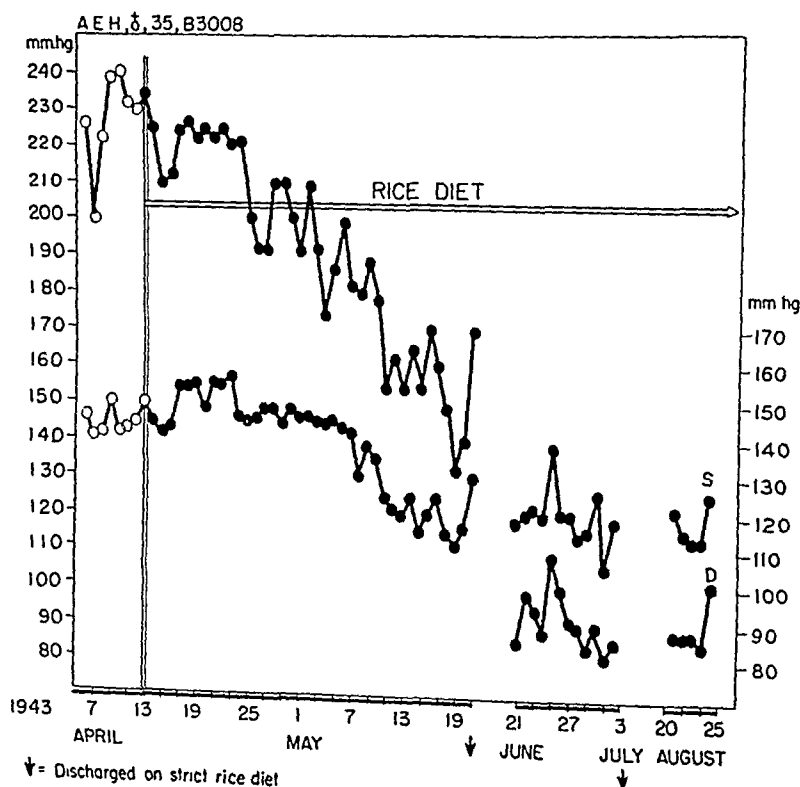


FIG. 16.

made. In January, 1941, he was seen in the Presbyterian Hospital. The blood pressure was found to be 200/140. One month later, the patient was seen in the Rockefeller Hospital with a blood pressure of 200/140. He was treated there by Dr. Henry Schroeder with tyrosinase until this had to be discontinued because of a severe shock-like reaction. As a matter of fact, this was the last patient whom Dr. Schroeder treated with tyrosinase. I like to show his record because Dr. Schroeder in the *American Journal of Medicine* in April of last year made the statement that the control periods preceding the rice diet might be too short to get an accurate base line for studying the effect of the diet. As is true for the majority of my patients, the base line for this patient was recorded by good observers not only over

are frequently told not to be concerned about their disease, unless some complication develops.

I believe the most appropriate time for treatment is before the more incapacitating complications of the disease have developed (cardiac breakdown, cerebral accidents, loss of vision and renal insufficiency). However, I will show you some typical electrocardiograms, chest films and eyeground photographs, which will illustrate that hypertensive vascular disease can be compensated to a great extent even when critical complications are already present.

Figure 14 shows the reversion of an abnormal electrocardiographic pattern to normal in a 35 year old man with hypertensive vascular disease of

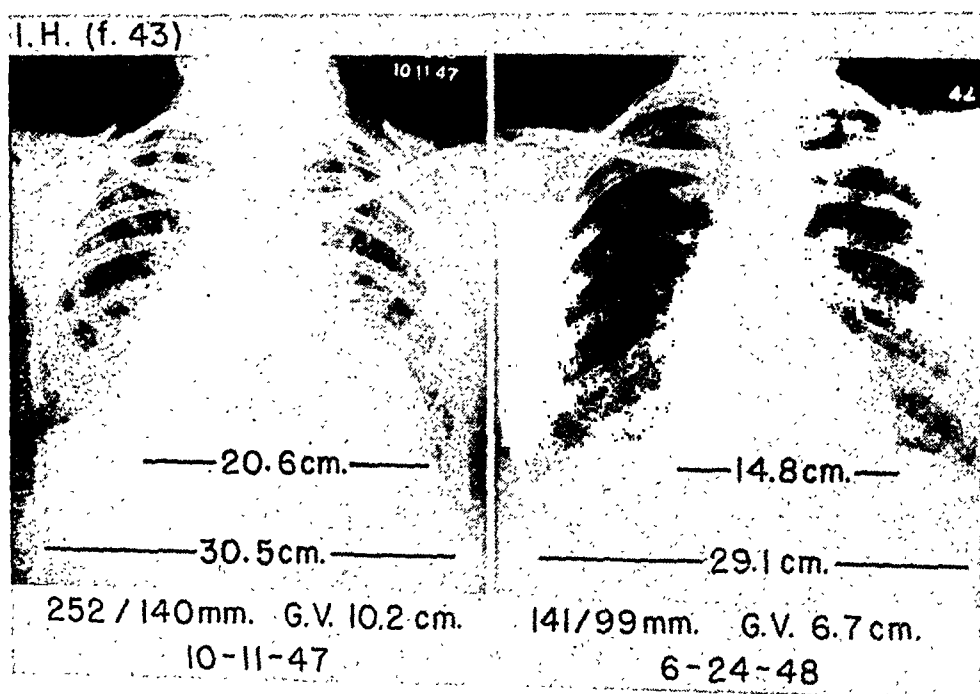


FIG. 18.

less than three years' duration. The change in the electrocardiogram is seen after 26 months on the rice diet. The blood pressure during this time decreased from an average of 205/122 to 150/103. Retinal hemorrhages and exudates disappeared. The deeply inverted  $T_1$  became upright; the electrical axis improved.

Figure 15 illustrates the time factor in the gradual improvement of  $T_1$ . The patient was a 35 or 36 year old woman. Hypertension was known to be present for about one year. In May, 1943,  $T_1$  was deeply inverted; in March, 1944,  $T_1$  was low inverted; in February, 1945, low upright; in May, 1946, normally upright. This case also shows that there is neither a simple relationship between blood pressure drop and  $T_1$  improvement nor between reduction in heart size and  $T_1$  improvement. The blood pressure decreased

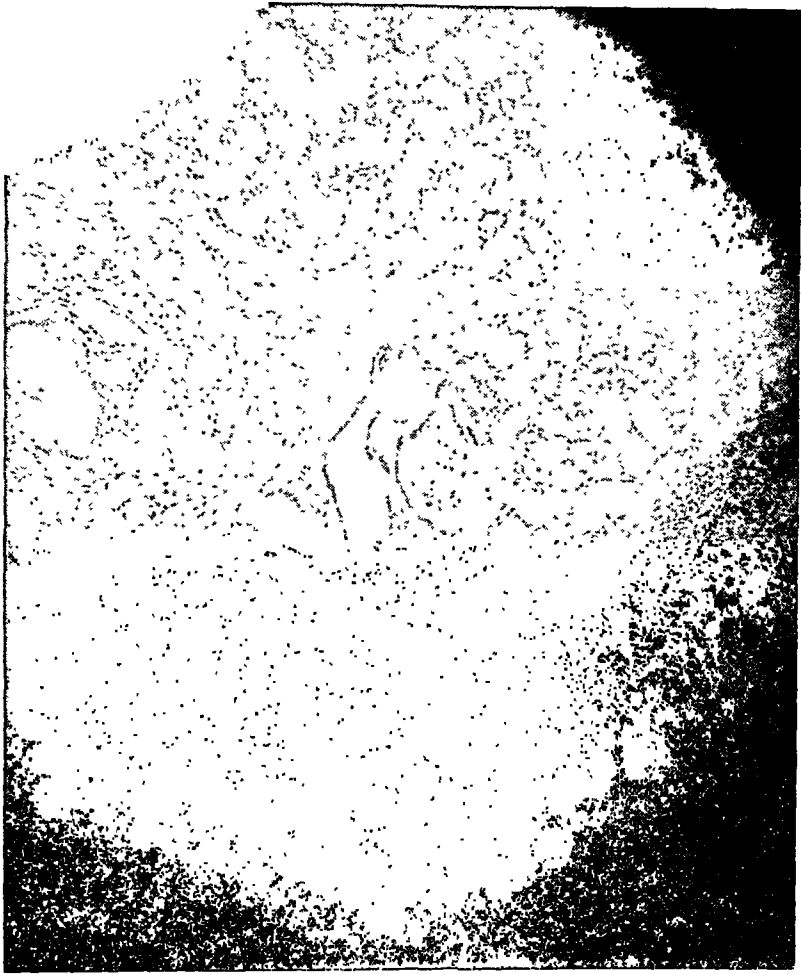


FIG. 3, c. Low power photomicrograph of mucosa near pyloroduodenal junction discloses a few dilated gastric glands containing mucus.

vember 3 and 18, 1946. Bismuth and mapharsen therapy was used November 27, 1946 to February 19, 1947. In April 1947 the blood Wassermann became negative but in August 1947, the test was reported as 4 plus. Numerous sedimentation rate determinations were done; the rate decreased from 8-30-69-76 on March 17, 1947 to 2-6-18-27 on August 1, 1947. Urinalysis on October 28, 1946 revealed no albumin or sugar but on February 28, 1947 a slight trace of albumin was found. On November 1, 1946 the tuberculin patch test was reported as 1 plus.

*Follow-up Notes.* The patient returned for roentgenographic studies of the upper gastrointestinal tract and chest on August 13, 1947. In the interval, however, the patient had experienced two "heart attacks" which confined him to bed most of the time. During these episodes auricular fibrillation was noted. Rather severe episodes of decompensation were combated with digitalis treatment but his cardiac status remained poor. His main complaint was dyspnea. The cardiac rhythm became regular but the rate remained rapid. Heart tones were rather distant and a very soft apical murmur could be heard. Gross pulsations of the lower left chest were visible. The blood pressure readings were 140/80 in the right arm and 115/82 in the left arm. Two plus ankle edema was noted. Electrocardiographic studies on August 11, 1947 showed changes either due to digitalis effect or left ventricular strain without axis shift.



A teleroentgenogram of the chest (August 13, 1947) revealed a moderate pleural effusion on the left side. The condition of the underlying lung was not ascertained. Pleural thickening was present in the right costophrenic angle. The heart seemed to be slightly enlarged to the left but the left cardiac border was partially obscured by the fluid in the chest. Slight dilatation of the aorta was evidently present.

Opacification of the esophagus yielded no evidence of obstruction. The mucosal pattern of the stomach was exaggerated throughout. No prolapse was present. Clinically, though, the patient complained of dysphagia. No retention studies were performed due to the physical condition of the patient.

We have been informed that this patient died October 13, 1947 at the Milwaukee County General Hospital. The description of the postmortem findings by Dr. J. M. Kuzma, Director of Laboratories, is as follows: "The patient had a small cell bronchiogenic carcinoma arising from the principal bronchus of the left lower lobe. This tumor had metastasized to the thoracic and abdominal lymph nodes, the liver and right adrenal. In addition to this, he had a golf ball sized infiltrating tumor involving the head of the pancreas. This was firmly attached to the duodenum but the common duct was in the superficial part of the tumor and not occluded. This tumor was primary in the pancreas and was an adenocarcinoma in sharp contrast to the small cell carcinoma of the lung. No metastases of this tumor were found. He also had multiple pedunculated polypi of the descending and sigmoid portions of the colon.

"Incidental findings were right lower lobe bronchopneumonia, a bifid pelvis of the right kidney and benign prostatic hypertrophy. There was chronic passive congestion of the liver and spleen. The heart weighed 330 gm. and was brown and flabby. No anatomic evidence of prolapse of the gastric mucosa was found."

*Comment.* Notwithstanding the postmortem findings, we believe that right heart failure was responsible for the herniation of the gastric mucosa in this patient with serologic evidence of syphilis. When the patient was examined roentgenologically for the first time in April 1947 there were undeniable clinical and physical signs of congestive heart failure. Roentgen examination revealed prolapse at this time. Shortly thereafter, an acute episode of cardiac decompensation and auricular fibrillation ensued. After two to three months of intensive symptomatic treatment, his cardiac status was considerably improved. The second roentgen examination of the stomach and duodenum on August 13, 1947 was performed in such a clinical state. At this time, the prolapse was almost indiscernible (figure 4, b). The progressive downward course, however, was due to malignant lesions in the lungs and pancreas with metastases to other sites, the patient ultimately succumbing to his cachectic state and heart failure with pulmonary edema. The examiner found no prolapse but the status of the gastric mucosa was not noted in detail.

This case demonstrates that prolapse can be reversible and can disappear with subsidence of edema and congestion and clinical improvement of the patient. Thus, early amelioration of gastric symptoms under treatment can indicate a favorable response to therapy.

*Case 4. History.* A male patient, aged 58, was referred as an outpatient for roentgen examination of the gastrointestinal tract and gall-bladder on January 18, 1946. The patient stated that he suffered from "heart trouble" and that two weeks previously he had vomited a cupful of blood. He had lost no weight but complained of indefinite upper abdominal discomfort. There was no relationship of symptoms to

diet. The patient reported that in March 1945 he had experienced pain in the chest and had dyspnea. He was taken to Emergency Hospital, Milwaukee, per ambulance where he received a number of "shots." He was dismissed the following day and returned to work. He continued to work until June 1945 when he was referred to St. Joseph's Hospital, Milwaukee for electrocardiographic study. The report stated "chronic coronary disease and serious myocardial impairment." He was subsequently advised to do only light work.

Roentgen studies were first performed on January 18, 1946 and again on February 8, 1946. Preliminary fluoroscopy of the chest in January revealed slight to moderate enlargement of the left ventricle. The barium filled esophagus was neither displaced nor encroached upon. The prepyloric and distal antral mucosal pattern was exaggerated, polypoid-like changes being present. Considerable mobility of the prepyloric mucosal folds was discovered and prolapse into the base of the duodenum (figure 5, a and b) was demonstrated during serial studies. No ulcer crater was seen and gastric motility was not delayed. A small diverticulum was seen in the second portion of the duodenum.

Oral cholecystography failed to opacify the gall-bladder. No radiopaque calculi were seen. The interpretation of lack of gall-bladder visualization in view of the cardiac status and prolapse was difficult. Barium enema studies revealed no pathologic lesions in the colon or terminal ileum.

The patient returned February 8, 1946 for repeat barium studies. No prolapse of the mucosa was seen at this time but the mucosal findings were essentially unchanged. The patient failed to return to the referring physician after the second series of roentgen studies but we have been informed that he died at home early in the year 1947.

*Comment.* In this patient with severe myocardial damage and mild right heart failure one can attribute the changes in the stomach to decompensation with subsequent prolapse. A bleeding point was not found during roentgen studies of the upper gastrointestinal tract. The site of origin of the hematemesis (cupful of blood) two weeks prior to roentgen-ray examination was not determined; there is at least a slight possibility that an erosion in the prolapsing portion of the mucosa of the stomach gave rise to such bleeding.

## DISCUSSION

That cardiac disease can be responsible for gastric complaints is not doubted. Since congestive heart failure occurs more frequently in the aged, prolapse of the gastric mucosa on such a basis could not be expected to occur with any great frequency in younger groups. Scott<sup>21</sup> does not mention the age of the patient who evidently died in heart failure and exhibited folds of gastric mucosa almost as edematous and mobile as those in one of our cases (case 2, figure 2, a and b). No roentgen studies were made in Scott's case. In an as yet unreported group of 50 successive cases of prolapsed gastric mucosa (A. M.,<sup>14</sup>), the youngest patient was 17 years of age and the oldest 69. Scott reported that prolapse of the mucosa was found in 1.04 per cent of the total number of gastrointestinal examinations performed, equalling the incidence of gastric ulcer in his group. In our experience this condition seems to be more frequent than benign gastric ulcer. On the other hand, herniated gastric mucosa occurred in several patients with peptic ulcers, as mentioned by Scott.

tory was not examined roentgenographically but the postmortem findings were so outstanding that no one could reasonably doubt that prolapse of the gastric mucosa had occurred during life. This patient had been a chronic asthmatic and entered the hospital with signs and symptoms of progressive right and left heart failure and died 36 hours after admission. Here, a cor pulmonale syndrome led to the right heart failure. The large, almost giant-sized gastric rugae could easily be swayed proximally or distally, in the latter case actually "flopping" across the pylorus (figure 2, a and b). The pyloric ring is clearly demarcated by arrows. On one hand, the folds lie proximally while, on the other hand, the markedly redundant folds are seen to extend beyond the pyloric ring into the duodenum. Microscopic sections (figure 3, b and c) reveal congestion and edema of the mucosa and submucosa and the presence of eosinophiles and plasma cells. The gross and microscopic findings are compatible with a diagnosis of "congestive gastritis."

The second group of patients, cases 3 and 4, confirmed neither at autopsy nor on surgery, presented clinical signs of right heart failure with cardiac enlargement. The first patient of this group (case 3) is an example of decompensated heart disease early in our period of observation. The roentgen appearance of the stomach and duodenum was due to prolapse of the gastric lining. Case 4 provides another example of arteriosclerotic heart disease, decompensation and prolapse of the gastric mucosa. This patient died soon after the roentgen studies. In all our cases, the "gastric" symptoms seem to be due, at least in part, to prolapse of the redundant folds.

Gastrointestinal symptoms in heart failure (especially of the right heart failure type) can be caused by involvement of different organs. Varying disturbances in physiology may thus result. However, there has been no mention in the literature regarding prolapse of the gastric mucosa as a possible cause of these symptoms in some cases. Gastric function is altered inasmuch as there is decreased motor, secretory and absorptive function in right heart failure with congestion. The total and free acid are lower than normal and there may be an acidity. In congestive heart failure, there is much mucus in the gastric secretions in addition to the low acid secretions (Bologna and Castadoni,<sup>4</sup> Niehaus,<sup>18</sup> Rehfuss<sup>19</sup>). Nevertheless, an acidity in the majority of instances gives rise to no symptoms and is compatible with perfect health (Best and Taylor,<sup>2</sup> A. J. Carlson<sup>5</sup>) except, of course, when associated with such pathologic states as pernicious anemia, carcinoma of the stomach, chronic gastritis and possibly prolapse of the gastric mucosa. Carlson states that the rôle of the gastric juice in the maintenance of health has been exaggerated to the neglect of normal motility. We may therefore conclude that the changes in the secretion are of minimal importance in producing symptoms in right heart failure. Whether involvement of the liver by the congestive process is enough to produce symptoms other than right upper quadrant pain is difficult to say. Probably, when the insults are severe or oft repeated, a "congestive cirrhosis" appears and symptoms can be caused by the central fibrosing process and the hepatocellular damage. Liver

3. BOCKUS, HENRY : Gastro-enterology, 1945, W. B. Saunders, Philadelphia.
4. BOLOGNA, A., and CASTADONI, A.: Gastropancreatic functions in cardiac patients, *Arch. ital. mal. app. diger.*, 1938, vii, 215-254. Abstract in *Jr. Am. Med. Assoc.*, 1938, cxi, 212.
5. CARLSON, A. J.: The secretion of the gastric juice in health and disease, *Physiol. Rev.*, 1923, iii, 1.
6. ELIASON, E. L., and WRIGHT, V.: Roentgen-ray diagnosis of pedunculated growths and gastric mucosa prolapsing through the pylorus, *Am. Jr. Roentgenol.*, 1926, xv, 295-322.
7. ELIASON, E. L., and WRIGHT, V.: Benign tumors of the stomach, *Surg., Gynec. and Obst.*, 1925, xli, 461-472.
8. FLAXMAN, N.: Gastrointestinal manifestations of heart disease, *Am. Jr. Digest. Dis.*, 1941, 8-10.
9. FORSELL, G.: Studies of the mechanism of movement of the mucous membrane of the digestive tract, *Am. Jr. Roentgenol.*, 1923, x, 87-104.
10. GOLDEN, R.: Antral gastritis and spasm, *Jr. Am. Med. Assoc.*, 1937, cix, 1497-1500.
11. HARRISON, TINSLEY : Failure of the circulation, 1935, Williams and Wilkins, Baltimore.
12. KOLETSKY, S., and BARNEBEE, J. H.: "Cardiac" or congestive cirrhosis, *Am. Jr. Med. Sci.*, 1944, ccvii, 421-430.
13. MEAKINS, J. C.: Intestinal and hepatic disorders in congestive circulatory failure, *Jr. Mich. State Med. Soc.*, 1940, xxxix, 474-480.
14. MELAMED, ABRAHAM : To be published.
15. MOORE, ROBT.: A textbook of pathology, 1944, W. B. Saunders, Philadelphia.
16. NIEHAUS, F.: Interchangeable signs and symptoms between circulatory and digestive symptoms, *Nebraska State Med. Jr.*, 1935, xx, 375-378.
17. PORTIS, SIDNEY : Diseases of the digestive system, 1944, Lea and Febiger, Philadelphia.
18. REES, C. E.: Prolapse of the gastric mucosa through the pylorus; surgical treatment, *Surg., Gynec. and Obst.*, 1937, lxiv, 689.
19. REHFUSS, MARTIN : Indigestion, its diagnosis and treatment, 1943, W. B. Saunders, Philadelphia.
20. REISMAN, D.: Myocardial disease and its gastric masquerades, *Jr. Am. Med. Assoc.*, 1928, xci, 1521.
21. SCOTT, WENDELL : Radiographic diagnosis of prolapsed gastric mucosa into the duodenum, *Radiology*, 1946, xlvi, 547-568.
22. WHITE, P. D.: Differential diagnosis of gastrointestinal and cardiac disorders, *Am. Jr. Digest. Dis.*, 1937, iv, 650.

The aerosol penicillin treatment, described herein, was undertaken solely as an office and home procedure in ambulant patients. When indicated, it was supplemented by the self-administration of aerosol penicillin at home, by oral penicillin, or by intramuscular injections of large doses of penicillin in oil and wax. Since the procedure was undertaken as a home and office method, no bacteriologic studies or penicillin blood level determinations were undertaken.

#### APPARATUS AND MATERIAL EMPLOYED

A number 200 Pen-i-sol nebulizer (Oxygen Therapy Company, Los Angeles, California), pictured below, was utilized. It consists of a glass nebulizer, rebreathing bag, and closely fitting oronasal face mask. The

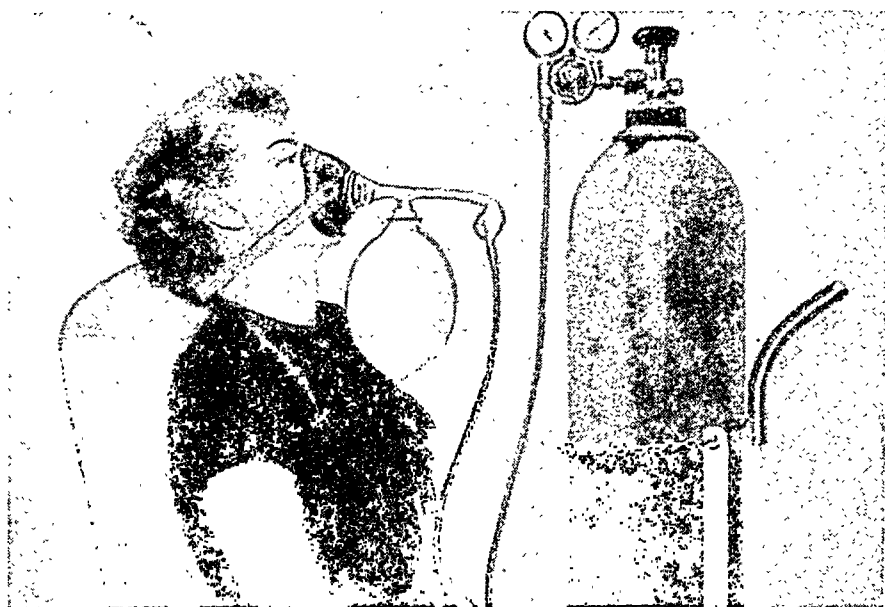


FIG. 1. The No. 200 Pen-i-sol Inhaler, with breathing bag and mask.

nebulizer is reported to convert penicillin solutions into particles finer than one micron in diameter. The glass nebulizer has a unique retort shape which allows the anterior wall of the nebulizing chamber to serve as the splash wall, preventing the droplets from being included in the stream of nebulin produced, and forcing any droplets back to the cone-shaped liquid area for nebulization. The closely-adapting mask minimizes waste and allows treatment through the nose or mouth or both. The breathing bag acts as a reservoir for comfortable breathing and retention of exhaled nebulin. No valve cut-off or "Y" is necessary. It has proved readily applicable to the very young or sick patient, since he may assume a passive rôle during the procedure.

The nebulizer is connected by rubber tubing to an oxygen tank. The penicillin is driven through the circuit under positive oxygen pressure at a

the foot ledge. The head rest was adjusted individually to permit a posture most suitable for proper respiration. Nasal tamponage was applied where shrinkage of the nasal mucous membrane was necessary to promote drainage and ventilation, and to permit the penicillin to reach the deeper infected tissues. However, it was repeatedly observed that a salutary shrinkage was achieved by the inhalation of oxygen alone, or in combination with aerosol penicillin. The use of the vasoconstricting nasal tampons, on the other hand, provided a more effective and lasting shrinkage.

The face mask was comfortably and securely fastened. Ten to twenty thousand units of aerosol penicillin were injected into the nebulizer. When a local antihistaminic effect was desired, as in cases of acute pollinosis, 0.2 cubic centimeter of 2 per cent pyribenzamine hydrochloride was added. When the patient required the antiasthmatic effect of epinephrine, it was added, usually as 0.2 cubic centimeter of 1:1000 solution of epinephrine hydrochloride. The 1:100 solution of epinephrine hydrochloride utilized by the aerosol technic caused a marked blanching and irritant effect on the nasal mucous membrane; its use, therefore, was abandoned. A group of patients, not included in this report, is being studied, using 0.25 per cent neosynephrine hydrochloride as the vasoconstricting agent.

The oxygen pressure gauge was set at 4.5 liters per minute. The patient was instructed to take deep inspirations every second or third breath, holding the inspiration as long as possible, followed by a deep and full expiration. He was cautioned not to force the respirations at a too rapid rate, in order to prevent the effects of hyperventilation. The average patient required five minutes to utilize completely 10,000 units of aerosol penicillin and 0.2 cubic centimeter of epinephrine or pyribenzamine. The time varied between five and eight minutes, depending on the age and size of the patient, the respiratory rate, amplitude of respirations, and the presence or absence of bronchial asthma. The patients were advised not to suppress coughing. Following this treatment, many asthmatic patients noted increased productive coughing, after which the respirations became wheeze-free. Occasionally, a few of those with shallow respirations developed coarse wheezing râles. This was felt to be due to bronchodilation with freeing of secretions into the alveoli and bronchial lumina. The wheezing usually disappeared promptly following expectorant coughing.

As a general rule, in patients with upper respiratory infections complicating a basic respiratory allergy, as hay-fever or allergic rhinitis, three daily treatments were adequate. As previously mentioned, supplemental penicillin was prescribed for home use orally or by inhalation. One hundred thousand units of penicillin were prescribed in 5 cubic centimeters of aerosol solution, to be administered with a De Vilbiss No. 40 nebulizer, 20 inhalations every half-hour. When the infection was of longer duration and greater intensity with definite evidence of acute sinusitis or bronchitis, 300,000 units of penicillin in oil and wax were injected intragluteally daily as

2. Acute pollenosis (hay-fever) with acute rhinitis and rhino-sinusitis—8 cases.

3. Allergic rhinitis with superimposed rhino-sinusitis—29 cases.

The criteria of response to aerosol penicillin were as follows:

1. Gross alteration in the appearance of the nasal mucous membrane.
2. Increase in vital capacity.
3. Reduction in blood sedimentation rates.
4. Apparent immediate clinical improvement, objectively and subjectively.
5. Comparison with the usual clinical course of previous respiratory infections not treated with aerosol penicillin.

A schematic record of the patients treated in this manner is shown in table 2.

It will be noted in table 1 that the distribution between the sexes is fairly equal in all decades except for the fourth where almost 50 per cent of the female patients is found. No particular significance is attached to this observation.

Twenty-five patients were treated with aerosol penicillin alone; 37 received combined aerosol penicillin and epinephrine hydrochloride; and 19 received aerosol penicillin and pyribenzamine hydrochloride.

It is of interest to record that, in this series, unpleasant side effects were noted in only two cases. In both, the reactions were attributed to epinephrine effect and consisted of palpitation of the heart. The first occurred in case 3, an extremely apprehensive male patient with chronic bronchial asthma. The second occurred in case 75, a young woman with bronchial asthma secondary to an acute upper respiratory infection, who was known to be extremely sensitive to epinephrine. The reactions were of brief duration, subsiding spontaneously.

None of the cases showed blackening of the teeth, gums, or tongue, or irritation of the upper respiratory tract, as has been reported by other observers. There were no immediate or delayed allergic reactions attributable to the aerosol penicillin. In fact, it is felt that the concomitant administration of epinephrine and pyribenzamine serves to reduce the possibilities for immediate constitutional reactions and to enhance the topical effect of penicillin.

To the best of my knowledge this is the first report where laboratory aerosol solution is the diluent used in the preparation of the penicillin.

It must also be noted that observations of the blood sedimentation rates are not a reliable index of the clinical efficacy of the procedure employed. No change in this rate should be anticipated unless one is certain that it is due entirely to infection within the respiratory tract which can be reached by adequate and effective concentrations of penicillin, and caused by penicillin-sensitive organisms. Where a remote focus of infection is responsible for

TABLE II—Continued

No.	In.	Sex	Age	Diag.	No. of Treat.	Sed. Rate	V.C. Bef.	V.C. Aft.	P.B.Z.	Ep. HCl 1:1000	Remarks
22	B. M.	M	46	B.A. A.R. H.F. S.	1	5	4.0	4.3			Improved; nasal pen.
23	G. R.	F	38	A.R. S. U.R.I.	3						Improved.
24	K. K.	M	8	B.A. U.R.I. S.	1						Improved; oral pen.
25	G. S.	F	40	B.A. A.R. S.	1	19		2.1			Temporary relief.
26	S. M.	F	21	B.A. U.R.I.	1		2.4	2.8		x	Improved; aer. pen. at home.
27	L. W.	M	14	B.A. S.	3						Improved; nasal pen.
28	J. K.	M	52	B.A. S.	4	15 15	2.5	2.6		x	Improved.
29	S. L.	M	6	B.A. U.R.I.	1						Improved.
30	M. D.	M	51	B.A. U.R.I.	2						Improved.
31	A. B.	F	29	B.A. A.R.	3	5	1.0	3.4			Improved.
32	R. E.	F	30	A.R. S.	1	18					Improved.
33	H. M.	F	46	B.A. A.R. H.F.	3	7	2.9	3.0	x		Improved.
34	C. C.	M	56	B.A.	1	6	3.0	3.1			Improved.
35	B. R.	F	33	A.R. H. F. S.	2	10 6			x		Improved.
36	L. E.	M	25	B.A. A.R.	4	10	4.0	4.2		x	Improved.
37	D. T.	M	7	H.F. U.R.I.	1						Improved.
38	D. W.	F	26	B.A. A.R. H.F.	4	18	1.8	2.5		x	Improved.
39	E. R.	F	16	B.A. H.F. U.R.I.	1						Improved.
40	B. S.	M	17	H.F. U.R.I.	1						Improved.
41	A. S.	F	31	A.R. S.	1	22 11	3.0	3.5			Improved; nasal and oral pen. at home.
42	M. S.	F	21	B.A. A.R. H.F.	16	25 18	2.8	3.0		x	Improved; aer. pen. at home.
43	I. B.	M	36	A.R. S. U.R.I.	3	7				x	Improved.
44	W. S.	F	49	B.A. A.R. S.	3	11	1.8	2.9		x	Improved; aer. pen. at home.



TABLE II—Continued

No.	In.	Sex	Age	Diag.	No. of Treat.	Sed. Rate	V.C. Bef.	V.C. Aft.	P.B.Z.	Ep. HCl 1:1000	Remarks
68	H. L.	M	22	H.F. U.R.I.	2				x		Improved.
69	R. C.	F	33	B.A. H.F. U.R.I.	6	22	3.2	3.3	x	x	Improved.
70	C. Y.	F	25	A.R. U.R.I.	1	8			x		Marked relief.
71	J. M.	F	39	U.R.I. A.R.	4	16			x		Improved.
72	S. B.	F	5	U.R.I. B.A.	2						Unimproved (uncoöperative).
73	E. G.	M	23	B.A. U.R.I.	1						Improved.
74	N. B.	M	4	A.R. U.R.I.	1						Slight improvement.
75	S. L.	F	14	B.A. U.R.I.	4	8				x	Marked improvement.
76	V. K.	F	42	A.R. H.F.	1				x		Improved.
77	L. H.	M	5	A.R. U.R.I.	2				x		Improved.
78	S. F.	F	37	B.A. U.R.I.	1						Improved; aer. pen. and pen. I.M.
79	M. H.	M	15	B.A. U.R.I.	1		2.2	2.2		x	Improved.

## KEY TO TABLE II

In.—Initials  
 B.A.—Bronchial asthma  
 A.R.—Allergic rhinitis  
 U.R.I.—Upper respiratory infection  
 Bronch.—Bronchiectasis  
 H.F.—Hay fever  
 S.—Sinusitis  
 Pulm.Fib.—Pulmonary fibrosis  
 Neph.—Nephritis  
 V.C.—Vital capacity  
 Bef.—Before aerosol penicillin

Aft.—After aerosol penicillin  
 P.B.Z.—Pyribenzamine hydrochloride  
 St.A.—Status asthmaticus  
 Br.—Bronchitis  
 Ep. HCl—Epinephrine hydrochloride  
 l.—liters  
 I.M.—Intramuscular  
 Aer. Pen.—Aerosol penicillin  
 Sed. Rate—Sedimentation rate  
 Diag.—Diagnoses

the sedimentation rate, this site may be unaffected by the penicillin, and the rate remains the same. Case 14 is that of a male patient with chronic glomerulonephritis whose sedimentation rate remained essentially unchanged even after large doses of penicillin intramuscularly in addition to aerosol penicillin; however, there was a slight reduction in the rate of fall during the first few minutes. The factors which influence the sedimentation rate are numerous and variable. Therefore, it is felt that its value is limited in appraising the benefits from the administration of aerosol penicillin to the series of patients under study. When the rapid sedimentation rate was due solely to the respiratory infection, the control and disappearance of the infection were frequently accompanied by a restoration of the sedimentation rate to normal.

## NITROGEN BALANCE STUDIES IN CHRONIC PEPTIC ULCER DISEASE \*

By THOMAS S. SAPPINGTON, M.D.,† and HENRY L. BOCKUS, M.D.,  
F.A.C.P., *Philadelphia, Pennsylvania*

IN recent years considerable interest has been shown in the nutritional aspects of peptic ulcer therapy. Some authors have not only reminded their readers that the ulcer patient has the same diverse food requirements as other persons, but have claimed special therapeutic value for "hyperalimentation" programs in the treatment of patients with uncomplicated peptic ulcer. Co Tui has emphasized the beneficial effect of a diet containing very large amounts of partially hydrolyzed protein.<sup>1</sup>

There are ample data to demonstrate the importance of a high protein intake in the treatment of a host of chronic illnesses and, in the convalescent period, a number of acute disorders. On the basis of a priori reasoning, therefore, it would appear likely that there would be a similar increase in the protein requirement in patients with *chronic* peptic ulcer. This should be true particularly in those with anorexia, voluntary or prescribed dietary restriction, vomiting or hemorrhage. There is available a rather simple procedure, the study of nitrogen balance, by which the protein requirement of such patients may be easily studied. A review of the literature reveals that there have been few such studies carried out on patients with peptic ulcer. Rather has emphasis been placed on the prompt relief of ulcer symptoms following the institution of the "hyperalimentation" or "high protein feeding" regimen. Symptomatic relief, however desirable clinically, does not prove the previous existence of a protein deficiency or the present existence of an increased protein requirement. The results obtained in this clinic in the management of uncomplicated peptic ulcer utilizing the hourly feeding milk regimen have been equally as good if not superior to the results reported following the use of the "hyperalimentation" regimen. We were of the opinion that if "hyperalimentation" is indicated in the therapy of uncomplicated ulcer its rationale should be substantiated by the demonstration of a nitrogen deficit in these patients. Consequently it seemed desirable to determine whether the average patient with uncomplicated ulcer admitted to the hospital was in nitrogen balance. Patients selected for nitrogen balance study had been hospitalized because of clinical evidence of activity of chronic peptic ulcer disease. Unfortunately patients with very early acute ulcers are seldom hospitalized in these days of crowded hospitals and hence could not be studied.

\* Received for publication March 25, 1948.

From the Gastrointestinal Service of the Graduate Hospital of the University of Pennsylvania.

Aided by a grant from the Julia Keim Memorial Fund.

† American College of Physicians Research Fellow in Internal Medicine.

TABLE I

Case 1, Female, Age 37

Date		Intake					Output				N Balance in Grams	Blood Examinations						Date	
		Diet Protein in Grams	Diet Fat in Grams	Diet N in Grams	Calories	Total Fluid in Ml.	Urine Volume in Ml.	Urine N in Grams	Stool Wt. in Grams	Stool N in Grams		RBC Count	Hb. in Grams	Hema- tocrit	Total Serum Protein in Grams in %	Total Serum Albumin in Grams in %	Total Serum Globulin in Grams in %		Blood Urea N in Ml. in %
2/8		66.2	32.2	10.5	1282	2140	1225	6.57	202	0.17	+3.8	4,100,000	13.5	41	6.80	3.95	2.85	9	2/8
2/9		51.5	6.6	8.2	846	2060	930	6.72	Soft	0.17	+1.4								2/9
2/10		68.8	11.6	11.0	1203	2200	lost	lost	brown	0.17	—								2/10
2/11		68.8	11.6	11.0	1203	2020	1625	10.50	formed.	0.17	+0.4								2/11
2/12		80.4	12.1	12.8	1413	1940	1450	8.26	No	0.17	+4.4								2/12
2/13		81.5	16.6	13.0	1324	2020	1095	8.26	blood,	0.17	+4.6								2/13
2/14		74.0	7.6	11.8	1164	1980	1700	7.61	pus or	0.17	+4.1								2/14
2/15		57.5	11.1	9.2	1085	2420	1300	8.74	mucus	0.17	+0.3	4,000,000	13.5	40	6.90	3.98	2.92	11	2/15
2/16																			2/16

TABLE II

Case 2, Male, Age 49

Date	Intake					Output				N Balance	Blood Examinations							Date
	Diet Protein in Grams	Diet Fat in Grams	Diet N in Grams	Calories	Total Fluid in Ml.	Urine Volume in Ml.	Urine N in Grams	Stool Wt. in Grams	Stool N in Grams		RBC Count	Hb. in Grams	Hema- tocrit	Total Serum Protein in Grams in %	Total Serum Albumin in Grams in %	Total Serum Globulin in Grams in %	Blood Urea N in Ml. %	
5/12	61.5	50.3	9.8	1054	1500	1200	9.06		2.55	-1.8	4,430,000	13.0	38	7.52	4.72	2.80	13	5/12
5/13	82.2	67.1	13.1	1408	1950	1250	8.95	1665	2.55	+1.6								5/13
5/14	68.3	55.8	10.9	1169	1675	1270	9.67	Light	2.55	-1.3								5/14
5/15	75.3	61.5	12.0	1290	1790	1455	11.02	brown	2.55	-1.5								5/15
5/16	46.5	38.1	7.4	798	1135	735	8.00	formed.	2.55	-3.1								5/16
5/17								No pus, blood or mucus			4,210,000	13.0	39	7.48	4.81	2.67	14	5/17
5/18																		5/18

In the hospital his symptoms responded readily to bed rest and feedings of four ounces of milk each hour while awake. Ten ml. of aluminum hydroxide gel were given each hour midway between the milk feedings. He also received two vitamin B complex capsules daily. For the period preceding and during the survey he received no other food.

*Comment:* The metabolic survey is reported in table 3. The patient was in slightly negative nitrogen balance during the test. The low urine nitrogen values are especially noteworthy as they indicate (in the presence of adequate urine volume) the low level of nitrogen excretion seen in patients receiving inadequate protein over a period of time. Under these circumstances the dietary intake should certainly have been greater, both to repair the already existing deficit and to provide a more liberal ration of protein for the maintenance of adequate nutrition after the deficit had been corrected.

*Case 4.* A male, 39 years of age. This patient had first suffered from duodenal ulcer in 1936, eleven years before entry to this hospital. A posterior gastrojejunostomy had been performed in 1938. Post-operatively he remained well until 1945 when he experienced a return of ulcer symptoms (burning periumbilical pain relieved by vomiting and by the taking of food). Eight months before admission there had been an episode of hematemesis and melena. Two months later he bled again. Four months before admission he was operated upon elsewhere and a lysis of the gastrojejunostomy was done. The patient was told he had had a marginal or jejunal ulcer. Post-operatively he remained well for three weeks, then began to have severe burning epigastric pain radiating to the back which was only slightly relieved by eating. The pain was especially severe at night, interfering with sleep. During the three months before admission to this hospital the diet had been restricted to fluids and light solids. It is estimated that during this period he received an average daily minimum intake of 55 gm. of protein and 2200 calories. He had lost six pounds during this time.

Physical examination revealed a thin individual with no gross evidence of nutritional deficiency. There was moderately severe mid-epigastric tenderness. Laboratory examination revealed normal urine and stools. The white blood cell count and differential cell count were normal. The van den Bergh, serum amylase, serum lipase and bromsulfalein dye retention tests were all normal. The prothrombin time was normal. Further data more pertinent to the metabolic study are reported in table 4.

During the first several weeks of the patient's course it was difficult to control his pain despite the strictest medical regimen. In fact, it was not until six days after the completion of the survey that the patient was consistently symptom-free. He received hourly feedings of four ounces of milk when awake. Ten ml. of aluminum hydroxide gel were given hourly midway between the milk feedings. In addition atropine, phenobarbital and vitamins were administered. He was kept at bed rest. On May 24, because of the persistence of pain, a constant intragastric milk drip was instituted by means of a nasal tube. This was discontinued after one day because of intolerance to the tube. The following formula was used on that one day for the tube feeding: 2040 ml. of skim milk containing 204 gm. of skim milk powder and 204 gm. of carbohydrate ("Dexin"). No other feedings were given on that day. The following day the patient was returned to the hourly milk regimen given by mouth.

Roentgen-ray examination revealed a normal chest and esophagus. In the stomach there was slight distortion of the mucosa in the region of the greater curvature in the mid-portion of the stomach which may have been the site of previous gastrojejunostomy. Slight coarsening of the mucosal pattern of the remaining stomach was

thought to be due to gastritis. The duodenal cap was moderately deformed with a pseudo-diverticular out-pouching of the greater curvature aspect of the mid-portion of the cap. The remainder of the cap showed moderate distortion of the mucosal pattern believed to be due to cicatrization from previous ulcer. The proximal jejunal loops were dilated and a niche 7.5 cm. distal to the ligament of Treitz was thought to represent a jejunal ulcer. Slight segmentation and flocculation were noted in the small bowel loops which probably represented disturbed motor physiology caused by nutritional deficiency.

*Comment:* The metabolic survey is presented in table 4. The entire fluid intake for each day represents milk except for one day (May 24) on which the tube formula was the only fluid given. It will be noted that only on two days of the milk feeding (May 22 and May 23) as well as on the day of the tube feeding was the protein intake adequate to effect a significant positive nitrogen balance. This may represent a temporary storage of nitrogen brought about by a sudden increase in the amount of nitrogen given. It will be noted that milk in ordinary amounts (two liters a day) did not supply sufficient protein to this patient to bring about a positive nitrogen balance if a protein deficiency existed. The low serum protein and serum albumin at the beginning of the survey definitely suggest a previous moderate protein deficiency.

*Case 5.* A male, 46 years of age. The patient had a history of duodenal ulcer disease for 21 years. The first symptom was a perforation which was closed. A gastroenterostomy was done at that time. Since then the patient has had occasional periods of epigastric distress relieved by food. During the two weeks before admission food gave incomplete relief. There had been no evidence of bleeding. His diet for the three years prior to admission had excluded meat (apparently on the advice of a physician), cabbage and fried foods. Review of the dietary history for the two months prior to his admission indicated a daily protein intake of 50 gm. and a caloric intake of 2400.

Physical examination revealed normal urine and stools. The leukocyte count and differential cell counts were normal. Fractional gastric analysis showed a grade 2 hyperacidity with hypersecretion and some motor delay. Insulin gastric analysis showed a maximum free acidity of 126 units and a total acidity of 154 units. Gastros-copy showed an essentially normal stomach. The stoma was not seen. Other laboratory results are listed in table 5.

Roentgen-ray examination on April 23 showed a normal chest and esophagus. The stoma of a posterior gastroenterostomy was seen three inches proximal to the pylorus with moderate distortion of the mucosa around the anastomosis. The duodenal cap was moderately deformed with a pseudo-diverticulum formation. An ulcer niche in the region of the greater curvature of the cap could not be excluded. The cap deformity was characteristic of scarring from ulcer. There was slight coarsening of the mucosal pattern of the proximal jejunum including the region of the anastomosis. A further roentgen examination on May 9 showed these same findings and in addition all of the small bowel loops were slightly dilated and there was moderate motor dysfunction, probably on a nutritional basis.

The patient's course in the hospital was satisfactory with rapid relief of his symptoms on a strict ulcer regimen, including bed rest, antispasmodics and sedatives. His diet consisted of hourly (when awake) five ounce feedings of the following formula with vitamin supplements: 120 gm. of skim milk powder and 120 gm. of carbohydrate added to 1800 ml. of skim milk. In addition he received protein

hydrolysate equivalent to 45 gm. of protein daily intravenously. He was afebrile throughout his stay.

*Comment:* The results of his metabolic survey are given in table 5. The patient was in normal nitrogen balance during this survey. Despite the dietary history and the question of nutritional deficiency raised by the mucosal pattern of the small bowel there was no storage of nitrogen at this high level of nitrogen intake. This patient was studied 14 days after the high protein diet was begun. It might be argued that a protein deficiency had existed originally and that this deficit had already been corrected by the high protein regimen given over a period of two weeks. We have found, however, that significant protein deficiency requires the prolonged administration of large amounts of protein for its correction.

### DISCUSSION

Of the five patients suffering from chronic peptic ulcer disease reported in this paper, Case 1 was found to be in consistent positive nitrogen balance and hence may be considered to have had a previous protein deficiency. Case 4 almost certainly had a significant protein deficiency. That conclusion, however, cannot be proved from the nitrogen balance data in table 4 because of the great daily variation in nitrogen intake and the possibility that the storage of nitrogen recorded on three days may have been temporary. Nevertheless, the low values for total serum protein and serum albumin at the outset of the study definitely suggest previous protein deficiency. Case 3 probably had had a previous protein deficiency but unfortunately insufficient protein was given to allow storage if such were to take place. However, the low urine nitrogen value in this patient suggests the presence of a previous protein deficit. Similarly in Case 2 inadequate protein was given to allow for nitrogen storage if such were to occur. The urine nitrogen value is not high but the patient is actually in slightly negative nitrogen balance because of a low protein intake and a high fecal nitrogen. Because the urine nitrogen in this patient is within normal limits it may be that no previous severe protein deficit existed. Case 5 gave no evidence of previous protein deficit and was in normal nitrogen balance with no nitrogen storage despite the large amount of nitrogen given. In brief, then, two patients had a previous protein deficit, one probably had, one probably did not have and one definitely did not have a previous protein deficiency.

All of our patients had been on suboptimal diets as far as protein was concerned. Anemia was not present in any patient. Total serum protein and serum albumin were definitely low only in Case 4 and borderline in Case 5. In Case 1, showing a definite protein deficit, the deficiency was apparently not sufficiently marked to be associated with an alteration of the serum proteins.

These studies suggest that 15 gm. of nitrogen daily might be a safe minimum intake for patients with uncomplicated peptic ulcer. This is

The oral administration of protein hydrolysates would seem to offer no advantage over whole protein in these patients.

#### ACKNOWLEDGMENTS

We are indebted to Dr. Arthur Finkelstein and his colleagues in the Department of Radiology of the Graduate Hospital for the roentgen interpretations. The success of the metabolic balance studies is due to the efforts of Miss Audrey Hurd and Mrs. Betsy Reith, nursing supervisors, and their associates. Miss Eleanor Cassel, Miss Nancy Daily and Mrs. Marie Weil, dietitians, supervised the weighing of diets and refusals and calculated the actual food intake. We are indebted to Miss D. Merritt Jones for technical assistance.

#### BIBLIOGRAPHY

1. TUI, C., WRIGHT, A. M., MULHOLLAND, J. H., GALVIN, T., BARCHAM, I., and GERST, G. R.: The hyperalimentation treatment of peptic ulcer with amino acids (protein hydrolysate) and dextri-maltose, *Gastroenterology*, 1945, v, 5.

an effort to make this study as comprehensive as possible no patient who met our requirements was omitted.

Only patients whose diagnoses were proved beyond reasonable doubt were studied. Patients suffering from concomitant metabolic disorders (such as diabetes, nephritis, and hepatitis) were excluded. Only patients who could cooperate in the collection of specimens were accepted. Thus some female patients were eliminated who were unable to collect urine and feces separately. Only adults were studied. No patient had had any surgical operation or major infectious illness within three months of the time of our study. Both of these events are known to affect nitrogen metabolism profoundly.<sup>5</sup> In order to avoid the pitfalls of short-term balance experiments it was necessary that whenever possible our subjects be hospitalized for a considerable period. Both ambulatory and bed patients were used. At times certain patients were febrile; this fact is noted in the protocols. No patient was studied at the time of menstruation, when pregnant or when congestive heart failure was evident. Many patients were anemic and underweight but appeared to be in fluid balance at the time of study.

All diets and refusals were weighed so that the net intake could be computed. Because of the long duration of many of the experiments (and the fickle appetite of the average patient with gastrointestinal disease), identical diets were not used. Free choice of food was allowed within the prescription of the attending physician. Standard dietetic tables were then used to compute the protein, carbohydrate, fat and caloric content of the food actually consumed. Previous studies indicated a maximum of 10 per cent variation between values for nitrogen calculated from the tables and values actually determined by analysis of food. Similar studies for fat indicated a maximum variation of 5 per cent. The value for protein in grams was divided by 6.25 to obtain the weight of equivalent nitrogen in grams. Although this factor assumes a constant nitrogen content of protein it is generally regarded as introducing little error when applied to mixed diets. Nitrogen given parenterally as protein hydrolysate or blood or plasma was added to the oral intake. In this instance the value for the total nitrogen content was used rather than that for free amino nitrogen. Many patients received supplementary feedings of a formula rich in carbohydrate and whole protein. No protein hydrolysate was given orally.

Daily measurement of fluid intake and output and frequent determination of the hematocrit and red blood cell count were done to note any significant diuresis or water storage, with the consequent temporary distortion of nitrogen distribution. Unfortunately blood volume studies were not possible.

The total nitrogen intake and the total urinary nitrogen output were calculated daily. Stool specimens were pooled for a period of several days and the total nitrogen content measured and divided by the number of days to give an average daily stool nitrogen value. The nitrogen balance was then determined by adding the daily stool nitrogen weight to that of urinary



passing four to six soft blood-streaked stools daily. Since then he lost nine pounds of weight, from a normal of 175 pounds, despite a good appetite. His height was 70 inches. He claimed to have eaten adequately during this period and a review of his diet for the month preceding admission indicated a protein intake of at least 70 grams, and a caloric intake of at least 2500.

Physical examination revealed a well nourished man with no abnormality other than a non-tender, palpable sigmoid colon. Sigmoidoscopy to a depth of eight inches showed a boggy membrane, easily traumatized, with a few scattered, punctate ulcers indicative of chronic ulcerative colitis of moderate activity with no polypoid changes. The urine was normal. The benzidine test for blood in the feces was strongly positive. Dysentery agglutinations were negative. Leukocyte counts and the differential cell count were normal. The sedimentation rate was 8 millimeters per hour (Westergren). The prothrombin time was 15 seconds or 75 per cent of normal concentration. Liver flocculation tests (cephalin-cholesterol, thymol and colloidal gold tests) were negative. The bromsulfalein dye retention test was normal. The van den Bergh test was negative. A fractional gastric analysis showed no free acid in the fasting specimen, hypoacidity and hypermotility. The Frei test was negative.

The roentgen-ray examination showed extensive ulcerative colitis in the distal transverse colon, descending colon and sigmoid without any spasticity or gross deformity of the colon. The esophagus, stomach and duodenum were normal. There was an occasional small bowel loop which appeared slightly distended or dilated. There was also slight segmentation in the small bowel.

During the first week after admission to the hospital there was a low grade fever rising to 100° F. but the patient was afebrile for four days preceding and during the test period. He was treated with a bland diet, bed rest, antispasmodics and ferrous sulfate. His weight on admission was 164.5 pounds and it rose to 168 at the time of discharge. During the test there was a decrease in the frequency of stools.

Comment: The metabolic survey is summarized in table 1a. Despite the small weight loss sustained by the patient, his good appetite, the history of nearly adequate diet and the appearance of being well-nourished, the nitrogen balance survey indicated a protein deficiency which was being corrected by a moderate protein intake during this test. The consistently low urine nitrogen values and the consistently positive nitrogen balance demonstrated a state of previous protein depletion. The stool nitrogen value was at the upper limits of normal.

Course between surveys: The patient was discharged on July 30, 1947. During the next two months he enjoyed good health. Because of the protein deficiency he was given a formula containing 90 gm. of calcium caseinate (containing 88 per cent protein) and 80 gm. of carbohydrate in a quart of milk. This, when taken with his regular high protein, low fat bland diet, provided 185 gm. of protein, about 100 gm. of fat and approximately 2500 calories. He also took one multi-vitamin capsule daily. His bowel movements decreased to an average of one every day. This was formed and passed without urgency, abdominal cramps, blood, pus or mucus. During the first month after his discharge he regained seven pounds of weight to return to his normal weight of 175 pounds. He was entirely asymptomatic. His nitrogen balance was then determined at home, approximately two months after the first study. The results are presented in table 1b.

Comment: Despite the fact that the patient had been taking a high protein diet (about 185 gm. daily) for the previous two month period, he was still storing nitrogen as indicated by the markedly positive nitrogen

balance. The urine nitrogen was considerably greater than in the previous survey but nevertheless about one-fourth of the high dietary nitrogen was being stored. The stool nitrogen on the other hand had returned to a normal value.

Course between surveys: The patient continued on the same high protein and high calorie bland diet *inasmuch as he was still deficient in protein. He remained asymptomatic.* He had normal bowel movements once or twice daily. His weight remained 175 pounds. His balance was again determined at home one month after the second study. The results are presented in table 1c.

Comment: Despite an unfortunate decline in the dietary intake on October 26 the survey demonstrates that the patient was still storing nitrogen in significant amounts. The proportion of intake being stored was about the same as in the previous survey. It is of interest (and thus far unexplained) that the patient's weight was not increasing coincidentally with the storage of protein.

Case 2. Male, age 39 years. This patient was admitted to the hospital on May 14, 1947. Symptoms of idiopathic chronic ulcerative colitis had been present without interruption for three years. He had experienced a sudden onset of diarrhea with as many as 14 stools a day. There was some blood-streaking of the stool but no gross bleeding. He suffered great urgency and severe cramps in the lower abdomen just before defecation. His appetite was excellent and in reviewing his diet it was estimated that he consumed about 85 gm. of protein and 2800 calories daily during the three months prior to admission. He had lost only 10 pounds of weight during the entire three years. He had a low grade fever intermittently and had had long courses of sulfadiazine, sulfathalidine and sulfaguanidine without improvement.

Physical examination revealed a healthy appearing, well-nourished man. His weight was 180 pounds and his height five feet nine inches. The only abnormal physical finding was the picture of moderately advanced chronic idiopathic ulcerative colitis and a benign rectal polyp seen on sigmoidoscopy.

Laboratory examination showed a sedimentation rate of 59 millimeters per hour, a normal bromsulfalein dye retention test, a normal leukocyte count and a normal differential cell count. His urine was negative and his stools gave a positive benzidine test for occult blood and contained some mucus but little pus.

The roentgen-ray examination showed the chest, esophagus, stomach, duodenum and small bowel to be normal. A barium enema showed extensive ulcerative colitis of the transverse, descending and sigmoid colon. There was no evidence of polyp formation.

His course in the hospital was afebrile. He was given a bland, high protein diet as indicated in table 3. Supplementary vitamins included 12 gm. of brewer's yeast, 100 milligrams of ascorbic acid and one halibut and viosterol capsule daily. He received 6 gm. of sulfathalidine daily. Protein hydrolysate was given intravenously in the form of 50 gm. of Amigen and 50 gm. of glucose each in a 5 per cent solution on the days indicated in the table. On this regimen he noted the gradual disappearance of urgency and cramps as well as blood-streaking of the stools. Some mucus persisted in his feces, but the number of daily movements had decreased to three at the time of his discharge. His discharge weight was 183 pounds or three pounds more than his admission weight. His first survey is reported in table 2a.

Comment: This patient showed a rather large positive nitrogen balance throughout the test indicating a state of protein deficiency despite the rela-

tive absence of clinical signs of nutritional deficit. The protein hydrolysate given intravenously in the latter part of the survey seemed to be utilized fairly effectively as indicated by a somewhat greater positive nitrogen balance during this time as compared with the preceding days when no intravenous hydrolysate was given. Comparison is difficult, however, because of variation in diet protein and fluid intake and output. It is of interest that the fecal nitrogen actually increased somewhat in the latter part of the survey despite the decrease in the number of stools.

Course between surveys: Following discharge from the hospital the patient continued to do well over the three and a third month period until the second survey was done. During this time he was consuming about 190 gm. of protein, 100 gm. of fat and 2500 calories daily. These figures included a formula containing 80 gm. of calcium caseinate (containing 88 per cent protein) and 80 gm. of carbohydrate in a quart of milk. The number of stools gradually decreased to two daily and were formed but soft. The patient was asymptomatic and returned to work. A benign rectal polyp was fulgurated through the proctoscope. Despite the ample diet the patient had gained only three pounds to reach his normal weight of 180 pounds. The second survey conducted at the patient's home is reported in table 2b.

Comment: The moderately high positive balance recorded for the three days is significant. It is suggested that the patient is still storing nitrogen after three and a third months of the high protein regimen. It is interesting that the fecal nitrogen is somewhat higher than during the first survey. The failure to gain weight corresponding to the nitrogen storage is unexplained.

Course between surveys: Due to a misunderstanding the patient reduced the protein content of his formula just after the second survey. For the next month his daily protein intake approximated 120 gm. or 19 gm. of nitrogen. He continued to be asymptomatic and the stools were formed but soft as before. His weight remained constant. One month after the second survey a third was made. It is summarized in table 2c.

Comment: The patient was in nitrogen balance during this test. The slight negative balance recorded is probably not significant at this high level of nitrogen intake. Had the previous daily intake of 30 gm. of nitrogen been maintained it is, of course, possible that the patient would still have been in positive balance.

*Case 3.* Male, age 31 years. The patient gave a history of chronic idiopathic ulcerative colitis of eight months' duration. During the first four months of his illness he suffered from diarrhea, consisting of five watery stools daily without blood, pus or mucus. Four months before entry he began to lose weight progressively and at the time of admission he weighed 147 pounds. His usual weight had been 177, and his height was 69 inches. He complained of generalized malaise and periodic epigastric pain which eventually gave way to crampy low abdominal pain. His appetite and food intake remained good. A review of his dietary habits showed a minimum intake of 100 gm. of protein and 3000 calories daily during his illness. His diarrhea became worse and two months before entry he was having 15 movements daily. Mucus and flecks of blood began to appear in his stools.

Physical examination showed a well-developed and nourished individual who did not appear ill. The only abnormal findings were generalized tenderness of the ab-

TABLE III  
Male, age 31. Chronic Idiopathic Ulcerative Colitis

Date	Intake				Output				Max. Temp. in °F.	Nitrogen Balance in Grams	Blood Examinations						Date
	Diet Nitrogen in Grams per Day	Diet Fat in Grams per Day	Diet Calories per Day	Fluid Intake, Ml. per Day	Urine Vol. in Ml. per Day	Urine Nitrogen in Grams per Day	Stool Weight Total in Grams	No. of B.M.'s Daily	Stool Nitrogen in Grams per Day		Hb. in Grams	Hematocrit	Serum Protein in Grams %	Serum Albumin in Grams %	Serum Globulin in Grams %	Blood Urea Nitrogen in Mg. %	
1/21	12.45	55	2200	1450	530	5.50	2207, Mucoid, purulent, bloody stool	9	7.60	98.6	13.0	40	6.56	4.12	2.44	9	1/21
1/22	18.72	89	2540	1505	650	5.71		9	7.60	98.4							1/22
1/23	21.67	99.6	2810	1742	785	5.50	2141 As above	8	8.3	98.2							1/23
1/24	21.75	100	2905	1710	1260	6.51		7	8.3	98.6							1/24
1/25	22.00	100	3005	2040	1740	5.93	4030 As above	6	7.85	98.6							1/25
1/26	21.85	100	3045	1745	945	5.62		6	7.85	98.0							1/26
1/27	21.50	100	2895	1520	605	5.50	As above	4	7.85	98.4							1/27
1/28	20.80	98	2844	1732	1100	5.74		3	7.85	98.8	13.0	40	7.60	4.32	3.28	10	1/28
1/29																	1/29

TABLE IVa

Male, age 47. Chronic Idiopathic Ulcerative Colitis

Date	Intake				Output				Max. Temp. in °F.	Nitrogen Balance in Grams	Blood Examinations					Date			
	Diet Nitro- gen in Grams per Day	Parenteral Nitrogen in Grams per Day	Diet Calories per Day	Fluid Intake, Ml. per Day	Diet Fat in Grams per Day	Urine Vol. in Ml. per Day	Urine Nitro- gen in Grams per Day	Stool Wt. Total in Grams			No. of B.M.'s Daily	Stool Nitro- gen in Grams per Day	RBC Count	Hb. in Grams	Hema- tocrit		Serum Protein in Grams %	Serum Albu- min in Grams %	Serum Globu- lin in Grams %
From 3/1 through 3/10 average diet of 14 grams of N, 50 grams of fat and 2500 calories, as well as 6 grams of parenteral nitrogen on alternate days																			
3/3		0	1077	1790	18.5	1125	7.08	1567	14	2.40	3,400,000	9.5	30	4.92	2.72	2.24		7	3/3
3/11	6.0	6*	2215	2200	51.0	1520	7.59	Liquid,	9	2.40	4,200,000	12.0	38	5.28	2.59	2.69		8	3/11
3/12	14.7	6*	2273	2420	49.0	1130	7.14	brown;	8	2.40									3/12
3/13	14.0	6*	2273	2420	49.0	1130	7.14	brown;	8	2.40									3/13
3/14	16.8	6*	2301	1670	42.5	1952	11.92	slight mucus	7	2.40									3/14
3/15	14.8	0	1674	1955	44.5	1050	7.92	and moder-	7	2.40									3/15
3/16	15.1	0	1644	2170	28.5	743	7.14	ate pus.	6	2.40									3/16
From 3/17 through 3/26 average diet of 16 grams of N, 45 grams of fat and 1800 calories, as well as 6 grams of parenteral nitrogen on alternate days																			
3/18	18.3	0	2354	2150	46.7	1520	7.72	3555	6	3.20	3,600,000	10.0	31	4.80	3.19	1.61		14	3/18
3/27	24.8	7.2x	2651	2480	46.7	1865	9.58	Formed,	5	3.20	3,600,000	10.0	34	4.80	2.86	1.94		14	3/27
3/28	19.3	0	2434	2590	59.1	2605	10.92	mucoïd	4	3.20									3/28
3/29	23.4	6*	2659	2630	48.1	2630	10.24	brown stool.	4	3.20									3/29
3/30	22.9	0	2599	2490	48.6	1655	8.25	No food,	4	3.20									3/30
3/31	18.2	7.2x	2504	2660	52.5	2710	13.00	little pus,	4	3.20	3,600,000	10.0	34	4.80	3.32	1.48		12	3/31
4/1	23.4	0	2547	2660	52.5	1694	8.29	no blood.	5	3.20									4/1
4/2	21.2	7.2x	2149	2670	54.5	2210	12.41		4	3.20									4/2
4/3	23.5	0	2187	2530	49.5	1685	9.11		4	3.20									4/3
4/4																			4/4
From 4/5 through 4/11 average diet of 22 grams of N, 60 grams of fat and 2200 calories, as well as 7.2 grams of parenteral nitrogen on alternate days																			
4/12	24.6	7.2x	2785	3165	63.9	3280	12.92	3594	5	4.43									4/12
4/13	21.4	0	3137	3105	94.7	2340	11.70	Formed,	4	4.43									4/13
4/14	26.6	7.2x	3290	3300	78.5	3194	12.88	mucoïd	3	4.43									4/14
4/15	26.7	0	3273	3105	86.7	1975	10.92	brown stool.	4	4.43	4,280,000	12.0	38	6.24	3.72	2.52		10	4/15
4/16	25.8	7.2x	3230	3180	73.0	2845	12.22	No food,	4	4.43									4/16
4/17	25.9	(0 Nitrogen) (1000 ml. 10% Glucose)	3334	3180	66.5	2900	10.62	little pus, no blood.	4	4.43									4/17

\* In form of "Amigen."

x In form of "Supprotin."

TABLE IVb  
Readmission of Same Patient Described in Table IVa

Date	Intake					Output				Max. Temp. in °F.	Nitrogen Balance in Grams	Blood Examinations						Date
	Diet Nitrogen in Grams per Day	Parenteral Nitrogen in Grams per Day	Diet Calories per Day	Fluid Intake, ml. per Day	Diet Fat in Grams per Day	Urine Vol. in ml. per Day	Urine Nitrogen in Grams per Day	Stool Wt. Total in Grams	No. of B.M.'s Daily			Stool Nitrogen in Grams per Day	RBC Count	Hb. in Grams	Hematocrit	Serum Protein in Grams %	Serum Albumin in Grams %	
8/11	3.26	6*	1061	2050	27	805	10.71	1563	24	1.61	3,999,000	11.5	34	5.36	3.25	2.11	15	8/11
8/12	14.20	0	1524	1690	66.1	385	5.65	Liquid with	21	1.61								8/12
8/13	9.07	6*	2052	2760	59.5	552	6.28	pus, blood,	22	1.61								8/13
8/14	8.00	0	1265	2100	38.0	395	5.85	and mucus	24	1.61								8/14
8/15	5.74	10.8#	1579	4000	29.1	590	10.80	in small	22	1.61								8/15
8/16	5.64	0.6#	923	2150	31.8	810	12.96	amounts	20	1.61								8/16
8/17	4.57	0	1053	1700	38.1	280	5.44		18	1.61								8/17
8/18	8.16	14.4x	1943	3500	47.4	1500	18.81		17	1.61								8/18
8/19	6.40	7.2x	1745	2600	46.2	1400	12.05		18	1.61								8/19
8/20	6.56	14.4x	1600	3200	47.0	1658	17.71		15	1.61								8/20
8/21	3.33	14.4x	1358	3400	47.4	1712	15.85	499	15	1.09								8/21
8/22	4.67	14.4x	1260	2400	47.4	1121	11.10	As above	14	1.09								8/22
8/23	7.75	14.4x	1740	3400	75.1	1520	15.60		12	1.09								8/23
8/24	7.00	14.4x	1760	2200	51.7	968	11.09		12	1.09	3,260,000	9.0	29	5.06	3.02	2.04	12	8/24
From 8/25 through 9/8 average diet of 8 grams of N, 60 grams of fat and 1600 calories, as well as 14.4 grams of parenteral N daily																		
9/9	10.2	0	1929	1760	98.8	1240	8.70	1420	10	3.05								9/9
9/10	17.3	0	2739	2160	107.7	1320	9.01	Soft brown,	10	3.05								9/10
9/11	33.9	0	3382	2330	149.7	1700	11.50	slightly	10	3.05								9/11
9/12	25.5	0	3011	2220	122.9	1388	4.37	mucoid. No	10	3.05								9/12
9/13	20.0	0	3100	2390	112.4	1640	4.05	blood, pus.	10	3.05								9/13
9/14	15.6	16*	2238	3760	112.9	2970	14.35	1267	10	1.60								9/14
9/15	17.0	0	2879	1910	168.4	970	14.12	Soft brown,	12	1.60								9/15
9/16	17.0	8*	2583	2830	170.8	1935	15.40	slightly	12	1.60								9/16
9/17	23.7	0	3573	1860	219.1	1245	13.38	mucoid. No	10	1.60								9/17
9/18	21.2	8	2871	2300	126.8	2000	16.40	blood or pus.	10	1.60								9/18
9/19	18.8	0	3016	2367	144.4	—	—	Occ. food	10	1.60	3,900,000	10.0	35	7.10	4.20	2.90	13	9/19
								particle.										

\* In form of "Amigen."

# In form of blood.

x In form of "Suprotein."

bromsulfalein dye retention test and the liver flocculation tests were normal. The dysentery agglutinations were negative.

His course in the hospital was stormy. His condition gradually deteriorated for the first seven weeks to reach a critical level in the eighth week (the first week in July). During the first six week period he received intensive sulfasuxidine and penicillin without benefit (in fact with decline, as just stated). On June 24 chemotherapy and antibiotics were stopped in view of their failure to relieve the patient's critical condition. His weight at this time was 131 pounds, representing a 27 pound loss since admission. It was therefore decided to direct greater attention to his nutrition. His appetite was poor and the most persistent urging was required to maintain even a moderate dietary intake. On this regimen clinical improvement began to be apparent during the second week of July with some reduction in temperature, pain and diarrhea. During the third week of July the daily maximum temperature elevation averaged 100° F. and the frequency of bowel movements was four daily. At the time of discharge, July 28, his weight was 125 pounds, he was having three bowel movements daily and except for weakness and the low grade fever he was asymptomatic. It was felt that he could convalesce more satisfactorily at home after more than two months in the hospital.

Roentgen-ray examination showed the chest, esophagus, and stomach to be normal. There was moderate deformity of the duodenal cap, the result of scarring from previous ulceration. No evidence of active ulcer was identified. The small intestines were normal. Examination of the colon by means of a barium enema showed an irregular marginal border of the colon extending from the proximal transverse colon to the sigmoid. Increased haustrations of the transverse and upper descending colon were demonstrated. The roentgen picture was that of a chronic ulcerative colitis involving the transverse, descending and sigmoid colon.

Comment: The metabolic survey is reported in table 5. During the period from May 14 through May 19 there was positive nitrogen balance despite the presence of fever and a low calorie intake. This finding demonstrates the existence of protein depletion. There appeared to be good utilization of the parenteral nitrogen. During the second period beginning on June 24 there also appeared to be good utilization of parenteral nitrogen. The low urinary nitrogen values in the latter part of this period indicate that a profound deficiency of protein had existed for some time and that the nitrogen metabolism was operating with great economy, as is, for example, the case in starvation. This is particularly striking when it is recalled that the patient was febrile throughout the entire survey. After June 29 he was dependent primarily upon his oral intake for nitrogen and it can be seen that although this was average in quantity it was grossly inadequate for the patient's needs. Ideally he should probably have continued to receive relatively large amounts of parenteral nitrogen throughout this period. It will be noted that a state of consistent small positive nitrogen balance preceded the clinical improvement by approximately two weeks. The stool nitrogen in this patient was the highest of any of our colitis patients (with the exception of the last period in the first survey of case 4). There was considerable purulent exudate present in these stools which is believed to account in part for their high nitrogen content.

## DISCUSSION

Each of the five individuals studied was found to be deficient in protein as indicated by the presence of a positive nitrogen balance. It is assumed that, in general, the normal adult individual does not store protein and that, under conditions of constant adequate nitrogen intake and cardio-renal competency, the nitrogen excretion is equal to the nitrogen intake; and it is further assumed that, under these same conditions, a positive nitrogen balance is evidence of preëxisting protein deficiency.<sup>8</sup> The existence of protein deficiency cannot be excluded by the absence of physical signs of malnutrition or by the presence of a normal concentration of serum protein. A diet of 70, 85 and 100 gm. of protein before hospitalization in cases 1, 2, and 3 respectively did not prevent a protein deficiency.

All of these patients were readily placed in positive nitrogen balance by the administration of a moderately large amount of protein. There was relatively little increase in urinary nitrogen excretion following increase in nitrogen intake, even in cases 4 and 5 in which the presence of fever might have been expected to increase urine nitrogen. This observation conforms to the pattern of economical utilization of protein found in patients chronically malnourished. On the other hand, patients suffering from acute infections lose large amounts of nitrogen in the urine early in the course of their illness and at this time even large amounts of oral and parenteral protein may not bring about positive nitrogen balance.

It is tempting to presume to assay definitively the utilization of parenterally administered nitrogen by these five patients. The conditions of our study, however, do not permit any final conclusion on this problem. As mentioned previously, Cuthbertson et al.<sup>7</sup> have found it difficult to determine the utilization of added dietary nitrogen in short term balance experiments because of a lag of as long as 15 days in the excretion of extra nitrogen following the addition of extra nitrogen to an adequate diet given to normal individuals. It should be emphasized again that our remarks on the degree of utilization of parenteral nitrogen by the patient described in case 4 are tentative.

The fecal nitrogen value varied considerably. During the period of most active diarrhea it ranged from 1.9 gm. to 8.3 gm. of nitrogen daily. It could not be correlated with the frequency of bowel movement or the severity of the illness. The highest value was found in one of the less ill patients (case 3). We believe abnormal fecal nitrogen in these patients is due to the presence of a purulent exudate and, to a lesser extent, blood, as is shown in the tables. Evidence of incomplete absorption of food was scanty. Gross food particles were observed only in case 4. In general there was no correlation between food and fecal nitrogen values. Measurement of the fecal total fat in these patients (to be reported) showed but a moderate increase (if any) above normal values. These findings are in keeping with the generally accepted belief that the colon is not the major site of absorption of foodstuffs



gen balance studies were done in the two patients who had been the least ill (cases 1 and 2). In case 1, after a daily nitrogen intake of approximately 29 gm. over a period of three months following discharge from the hospital, the protein deficiency had not yet been corrected, as is shown by the positive nitrogen balance. In case 2 the protein intake was similar to that of case 1. Between 100 and 130 days were required to restore protein equilibrium, in which the nitrogen excretion equalled the intake. Similarly a patient with chronic duodeno-jejuno-ileitis with severe wasting before hospitalization was studied at intervals for five months after the relief of symptoms. Throughout this period she consumed between 20 and 25 gm. of nitrogen and about 2500 calories daily and remained essentially asymptomatic. Frequent balance studies (including the last) during this period showed consistent positive nitrogen balance, averaging 12 gm. of nitrogen daily. (Detailed studies of this patient are to be reported in another paper.) In these three patients there was no gain in weight during the last two months of this prolonged nitrogen storage—a fact difficult to explain. These observations, if generally confirmed, suggest that many of these patients never entirely repair their protein deficits when given diets containing moderate amounts of protein, ordinarily considered adequate. This state of chronic deficit may be a very important factor in predisposing them to recurrence of colitis set off by intercurrent infections, dietary upsets, emotional turmoil, etc.

#### SUMMARY

The over-all protein metabolism of five patients suffering from chronic ulcerative colitis has been studied. All were found to have protein deficiencies as determined by nitrogen balance study on admission to the hospital. Three of the patients presented no signs of undernutrition on physical examination.

Positive nitrogen balance could be achieved and maintained in these patients by giving diets moderately high in protein with or without the parenteral administration of protein hydrolysates or blood. Although difficult to prove by observation under clinical conditions, it was our opinion that parenterally administered protein hydrolysate was relatively well utilized by these patients. The hydrolysate was probably not as beneficial as an equivalent amount of protein given orally, but was advantageous when used to supplement a high oral intake of protein.

Large fecal losses of nitrogen were not common and when present seemed to be due to purulent or bloody exudate rather than unabsorbed food (even when the dietary intake was high).

No patient improved clinically unless positive nitrogen balance had been achieved and maintained. In four instances positive nitrogen balance preceded clinical signs of improvement by several weeks. Follow-up studies on two of these patients and another to be reported elsewhere indicated that high protein feeding for several months may be necessary to correct the protein deficit in these patients.

# THE SHOULDER-HAND SYNDROME: A COMPLICATION OF CORONARY ARTERY DISEASE\*

By A. W. HILKER, M.D., *Eau Claire, Wisconsin*

THE condition of reflex dystrophy of an extremity following an injury has been discussed fully by many authors in the past 70 years. As early as 1877, and later in 1883, Wolff<sup>1, 2</sup> discussed trophic changes in the limbs following resection of a joint or following infection. In 1895 Kümmell<sup>3</sup> reported six cases of bone atrophy following injury. In 1900 Sudeck<sup>4, 5</sup> described fully the post-traumatic osteoporosis which is known as Sudeck's atrophy; in 1902 he wrote further on this subject and since that time there has been much in the literature with general agreement that this condition is a reflex dystrophy.

Recently de Takats<sup>6, 7, 8</sup> has written extensively on causalgia, post-traumatic, and its relation to Sudeck's atrophy and reflex dystrophy and he further describes its mechanism. In more recent years Sudeck's atrophy, causalgia or reflex dystrophy of an extremity involving a shoulder and hand has been noted as resulting from other causes than trauma. In 1948, Steinbrocker, Spitzer, and Friedman<sup>9</sup> published a most comprehensive study of the multiple conditions that produce a reflex dystrophy of an upper extremity; all, however, simulating the post-traumatic syndrome. The later authors' report was based on 42 cases of reflex dystrophy of the upper extremity developing from the following conditions: After myocardial infarction, post-traumatic, post-hemiplegic, post-herpetic and with cervical osteoarthritis. There were four cases with multiple or inconclusive etiology and 11 cases in which no apparent cause was found, and which were listed as idiopathic. Of the 42 cases reported, nine were a sequel to myocardial infarction. This great variety of causes originating far apart from each other, and apparently involving the involuntary nervous system without definite segmental distribution, has given rise to the recent and most acceptable neurophysiological explanation, namely, involvement of the internuncial pool in the spinal cord. Lorente de Nó<sup>10</sup> advanced this theory in 1938 in his article, "Analysis of the Activity of the Chain of Internuncial Neurons." In 1943 Livingston<sup>11</sup> elaborated on this concept as a neurophysiologic interpretation of causalgia.

Steinbrocker et al.<sup>9</sup> summarized this mechanism in the following statement, "Recent physiologic investigation shows this internuncial pool to be an extensive network of interconnecting neurons in the central gray matter, extending over many segments. At these levels potential connecting pathways are formed between incoming impulses and motor neurones of either the sympathetic (posterolateral) or anterior horn cells." This concept is gen-

\* Received for publication November 13, 1948.

From the Department of Internal Medicine, Midelfart Clinic, Eau Claire, Wisconsin.

The patients with angina pectoris, however, only develop the syndrome if there is evidence of myocardial insufficiency. It may occur with severe coronary artery disease without clinical evidence of an infarction, but it usually manifests itself more definitely following an occlusion. There is no predilection for involvement of any one side of the body; either the left or right upper extremity or both may become involved. Occasionally one shoulder and both hands, or both shoulders and one hand are affected. Not infrequently a first symptom is a painful shoulder and a sore, tender, swollen hand. The ultimate result is a contracted shoulder and marked trophic changes of the hand. At the onset the hand or hands become swollen, painful, tender and stiff, with various shades of discoloration ranging from red to blue. The hand or extremity is usually warmer than the other parts of the body. The skin of the fingers loses its normal wrinkles and movement is limited and painful. In some of the less severe cases physical findings may be few, yet the patient's symptoms regarding his hands may be great; not until a later date is it really apparent that a pathologic process existed.

In the first stage the hand is swollen, painful, tender, warm and discolored. A patient may recover completely at this point or he may go into a second stage. Here the swelling disappears but the pain and stiffness are persistent and progressive and movement becomes further limited. The hand usually becomes colder, the skin becomes thin and more attached to underlying structures. The muscles become atrophic and the hand loses its normal softness, the tendons are thickened and tender and the palmar fascia may be involved. A roentgen-ray of the hand shows marked trophic changes of the metacarpal and hand bones. If the shoulder is involved, there is a burning, painful joint, with limitation of motion and roentgen evidence of trophic changes of the end of the humerus. Even at this stage the pathology may be interrupted and partly reversible. Most persons who have gone on to this second stage, however, are crippled permanently to some degree. The process may continue and go into a third stage.

The end result or third stage is a contracted, claw hand with thickening and shortening of the tendon sheaths and palmar fascia, atrophy of the muscles and further trophic changes of the bone. The hand is cold, hard, stiff, contracted and immobile. The hand at this stage is very similar to that seen in reflex dystrophy following a severe injury to the arm, and the bone changes resemble those of Sudeck's atrophy.

#### DISCUSSION OF CASES

The series consisted of 11 cases of coronary artery disease, nine of them with myocardial infarction, in whom ischemic involvement of an arm and hand occurred, resulting in varying degrees of trophic changes. Some changes were minor and apparently reversible; others were marked, deforming, and permanently incapacitating.

Two patients had coronary insufficiency with angina pectoris but without

motion in the shoulder affected and 85 to 90 per cent loss of function in the hands. In both cases the peripheral circulation seemed adequate.

In case 3, the patient developed a massive pulmonary effusion secondary to multiple left pulmonary infarction following a coronary thrombosis. This patient had had prolonged hypotension and evidence of forward failure for several weeks and during this time the shoulder-hand syndrome progressed to the far advanced stage. Subsequently there was resolution of the chest condition and adequate myocardial function, but after several months there was little improvement in the trophic changes of the hand and shoulder. Case 4 developed a pulmonary complication following Dicumarol therapy for her myocardial infarction. Daily prothrombin times were taken prior to the administration of Dicumarol. Several days following the infarct the prothrombin was found to be 12 per cent; simultaneously the patient developed a pericardial friction rub that persisted for many days. During that week the left chest became dull to percussion and a roentgenogram revealed a massive effusion. It was suspected that she had a hemopericardium and that the effusion was also bloody secondary to the very low prothrombin. This patient also had prolonged hypotension and evidence of forward failure for several weeks and during this time the shoulder-hand syndrome began and progressed to an advanced stage. Subsequently there was resolution of the chest condition and an adequate myocardial function developed, but this patient, too, has had little improvement in the trophic changes of either the shoulder or the hand.

Cases 5 to 8 inclusive, with myocardial infarction, three anterior and one posterior, all developed hand pathology. Two of these also had shoulder involvement. Each had a painful, swollen, stiff hand that developed three to six weeks after the infarction and each had a varying degree of residual after one to one and one-half years. These residuals range from tender, thickened tendons to atrophy of muscle and up to 20 per cent loss of motion. Although this group shows least involvement the symptomatology here is nevertheless very disturbing.

One case, number 9, a man 44 years of age, had a severe anterior myocardial infarction. Five weeks after the infarction, he developed a swollen, painful left hand. This went through various changes until presently, eight months post-infarction, there is no residual, with complete return of function. There is no evidence of myocardial insufficiency.

Still another patient, case number 10, had coronary artery disease with angina and he developed a painful right shoulder with a mildly aching right hand but without appreciable physical changes. One year later, however, he developed a severe posterior myocardial infarction and three weeks after this there occurred a marked exacerbation of the right shoulder pain and definite swelling, discoloration and painful limited motion of the fingers of the right hand. Presently, six months later, the patient is suffering from a contracted right shoulder, being able to elevate his arm only  $120^{\circ}$  and also from a trophic hand with 25 per cent loss of finger flexion. The patient has little

If one accepts the most recent neurophysiological work regarding the etiology of this syndrome, then one might reason that with a myocardial infarction there is a disturbance of the electrical conduction of the myocardium which may set up a response in the sympathetic nerve plexus of the heart. This response is then carried through the inferior, middle and superior cardiac nerves to their respective cervical ganglions. The stimuli may then be transmitted to the spinal cord and into the internuncial pool. In the internuncial pool the stimuli may travel upward into the anterior horn cells, causing disability of the shoulder, or downward into the lateral horn cells or sympathetics innervating the whole upper extremity in the region of T<sub>1</sub> and T<sub>4</sub>. It may be reasoned that anoxia with defective local tissue nutrition might be the possible stimulus that perpetuates the condition, at least to far advanced changes. The correction of anoxia and of the defective local tissue nutrition would then be responsible for interrupting this cycle and reversing the process.

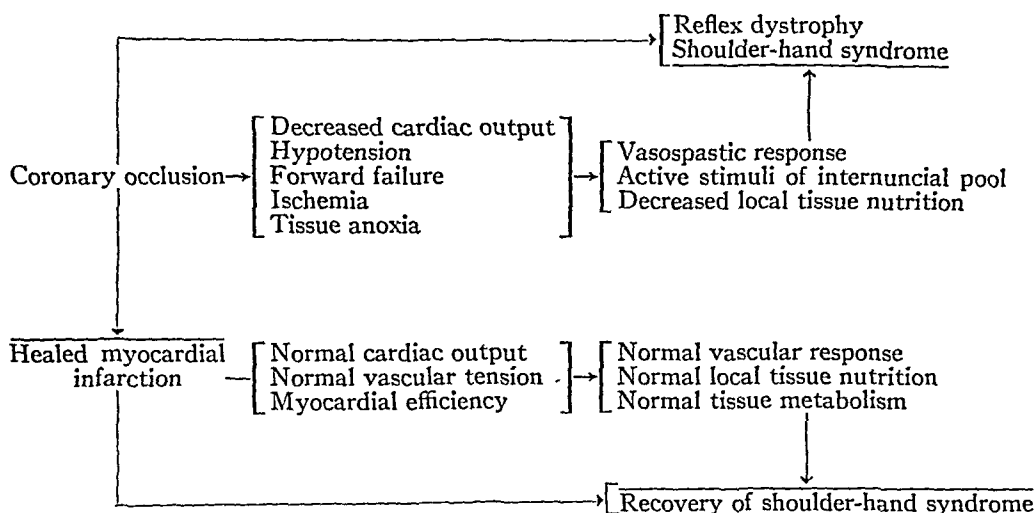


FIG. 1. Possible factors in the development of the shoulder-hand syndrome following myocardial infarction and the factors that may reverse the process.

The accompanying diagram (figure 1) illustrates the possible factors in the development of the shoulder-hand syndrome following myocardial infarction and the factors that may reverse this process. In any severe myocardial infarction there is decreased cardiac output, hypotension, evidence of forward failure with ischemia and tissue anoxia. These factors lead to a decreased local tissue nutrition and this decreased local tissue nutrition may be the active stimulus to the internuncial pool which sets up a vasospastic response leading to the reflex dystrophy of the shoulder-hand syndrome.

On the other hand, when the myocardium becomes healed and a normal cardiac output is restored, there is normal vascular tension. This then leads to normal tissue metabolism, normal local tissue nutrition, and therefore, one would expect a normal vascular response which in turn would lead to the recovery of the shoulder-hand syndrome. If, however, the pathologic process

5. SUDECK, P.: Ueber die akute (trophoneurotische) Knochenatrophie nach Entzündungen und Traumen der Extremitäten, *Deutsch. med. Wchnschr.*, 1902, xxviii, 336-338.
6. DE TAKATS, G., and MILLER, D. S.: Post-traumatic dystrophy of the extremities—a chronic vasodilator mechanism, *Arch. Surg.*, 1943, xlv, 469-479.
7. MILLER, D. S., and DE TAKATS, G.: Post-traumatic dystrophy of the extremities—Sudeck's atrophy, *Surg., Gynec. and Obst.*, 1941, lxxv, 558-581.
8. DE TAKATS, G.: Nature of painful vasodilation in causalgic states, *Arch. Neurol. and Psych.*, 1943, 1, 318-326.
9. STEINBROCKER, O., SPITZER, N., and FRIEDMAN, H. H.: The shoulder-hand syndrome (reflex dystrophy of the upper extremity), *Ann. Int. Med.*, 1948, xxxiii, 22-52.
10. LORENTE DE NÓ, R.: Analysis of the activity of the chain of internuncial neurons, *Jr. Neurophys.*, 1938, i, 207.
11. LIVINGSTON, W. K.: Pain mechanisms: a physiologic interpretation of causalgia and its related states, 1943, Macmillan Company, New York.
12. HOWARD, T.: Cardiac pain and periarthrits of the shoulder, *Med. Jr. and Rec.*, 1930, cxxxi, 364-365.
13. EDEIKEN, J., and WOLFERTH, C. C.: Persistent pain in the shoulder region following myocardial infarction, *Am. Jr. Med. Sci.*, 1936, cxc, 201-210.
14. LEECH, C. B.: Painful shoulder in association with coronary artery disease, *Rhode Island Med. Jr.*, 1938, xxi, 104-106.
15. ASKEY, J. M.: The syndrome of painful disability of the shoulder and hand complicating coronary occlusion, *Am. Heart Jr.*, 1941, xxii, 1-12.
16. MEYER, J. C., and BINSWANGER, H. F.: Recent myocardial infarction followed by involvement of the joints of the hand and wrist, *Am. Heart Jr.*, 1942, xxiii, 715-718.
17. KEHL, K. C.: Dupuytren's contracture as a signal to coronary artery disease and myocardial infarction, *Ann. Int. Med.*, 1943, xix, 213-223.
18. JOHNSON, A. C.: Disabling changes in the hand resembling sclerodactylia following myocardial infarction, *Ann. Int. Med.*, 1943, xix, 433-456.

The work of the heart is increased in hypertension and roughly in proportion to the systolic pressure. As the hypertension continues, the left ventricle of the heart hypertrophies but the coronary blood supply tends to lag behind. Since the hypertensive heart functions at a higher than normal base, it possesses a distinctly reduced reserve. Moreover, the coronary arteries of hypertensives show a much higher incidence of arteriosclerosis than normotensives of similar age groups. These facts constitute the pathophysiologic bases for the cardiac complications of myocardial insufficiency and infarction.

The cerebral arteries have thin walls and are poorly supported by brain tissue since they lie in the perivascular spaces. Next to the coronary arteries and the aorta, the cerebral vessels are most subject to arteriosclerosis. The arterial branches supplying the region of the internal capsule are especially thin-walled and in direct line with the pressure wave from the heart. These facts form the pathophysiologic bases for the frequency of cerebral hemorrhage in hypertension.

With the passage of years progressive renal arteriosclerosis causes a gradual decrease in renal function, although in the great majority of essential hypertensives renal function is still comparatively satisfactory when the hypertension is terminated by death from cardiac insufficiency or infarction, apoplexy, intercurrent disease, or old age. However, approximately 10 per cent of essential hypertensives succumb to renal failure. So-called malignant hypertension may be present from the start, or benign hypertension may suddenly change into the malignant form. The difference between benign and malignant hypertension is probably primarily quantitative with reference to severity and time. On the other hand, the typical lesion of benign hypertension is arteriosclerosis and arteriolosclerosis, whereas that of malignant hypertension is arterionecrosis and arteriolonecrosis. The renal vessels, as well as those of other tissues and organs are involved in the necrotizing process. As a consequence renal blood flow and renal functions are markedly reduced with resulting uremia and death.

(b) *Pathogenesis.* Recent studies have confirmed the facts that essential hypertension appears more frequently in certain families and in stocky, pyknic, overweight individuals. However, heredity and body type must operate through pathophysiologic mechanisms. In spite of recent extensive and productive laboratory and clinical research, the pathogenesis of essential hypertension is still obscure. This is true even though there are occasional categorical statements in the literature to the effect that essential hypertension is due to an increased secretion of the pressor enzyme, renin, by the kidney.

From the standpoint of pathogenesis, essential hypertension is probably a generic classification. The hypertensions due to pheochromocytomas, adrenal cortical tumors, and renal abnormalities were once classified under essential hypertension. As our knowledge increases, other species of hypertension will undoubtedly be split off. Current research on pathogenesis

appear to have normal renal blood flows, so that the significance of renal ischemia in the pathogenesis of essential hypertension, as in experimental renal hypertension, is still unsettled.

There is some evidence suggesting that injections of the corticotropic hormone of the anterior pituitary may produce experimental hypertension in rats, presumably through stimulating increased secretion of adrenal cortical hormones, one or more of which may be directly vasoconstrictor or may possibly in turn increase the output of renin from the kidney. The maintenance of experimental renal hypertension is dependent upon adequate anterior pituitary and adrenal cortical functions. On the clinical side, a minority of patients with essential hypertension show an increased tolerance to insulin, large doses of desoxycorticosterone have produced hypertension in normotensive humans, sodium chloride metabolism is mildly altered in essential hypertension, and marked sodium chloride restriction has an antihypertensive effect in some essential hypertensives. These findings suggest but do not prove that a certain undetermined proportion of patients with essential hypertension may have increased adrenal cortex function as the pathogenetic basis for their elevated blood pressure. The cortex might differentially produce an augmented secretion of an as yet unknown cortical steroid with a predominant vasoconstrictor effect and with minimal effects on carbohydrate and salt metabolisms.

(c) *Treatment.* Recent advances in treatment have likewise not been decisive. There is still no "magic bullet" for the therapy of uncomplicated essential hypertension. Psychotherapy (by a psychiatrist, if necessary) is still an important adjunct. The benign character of essential hypertension in certain patients is sometimes forgotten. Any program of mental and physical rest outlined for an essential hypertensive should be individualized and guided by every-day, practical considerations. Intermittent courses of one of the barbiturates will remove some of the nervous tension. Certain new drugs which are capable of blocking vasoconstrictor nerve impulses are being tested in the treatment of essential hypertension. In this group are tetraethylammonium chloride, dibenamine, dihydroergotamine, dehydroergoclonine, and certain *Veratrum* derivatives. Tetraethylammonium chloride has already proved of value in the study of essential hypertensives to determine their suitability for sympathectomy.

Although certain renal extracts have proved of therapeutic value in experimental renal hypertension, no one has yet prepared a consistently potent, sufficiently purified renal extract suitable for trial in human hypertension. Certain marine and fish liver oils and fractions thereof have been studied therapeutically in experimental renal hypertension and have been shown inconstantly to contain variable amounts of an orally effective antihypertensive agent which is not vitamin A. Years ago radical restriction of protein and salt was recommended by some authorities. Recently a low protein, low salt diet consisting principally of rice and fruit has been recommended on the thesis that the kidney is involved pathogenetically in essential hyperten-



Thiocyanate may have a slight sedative action or may act merely through a nonspecific, toxicological depressor effect.

The estrogens and androgens have no specific effect against essential hypertension, although they will relieve climacteric symptoms which may aggravate a concomitant hypertension. Vitamin A, members of the B complex, and vitamins C, E and K have all been found to be without value in the treatment of essential hypertension. The same may be said for histamine, mecholyl, pancreatic extracts, garlic and parsley, liver extracts, and other preparations, even though some of these are still advertised and sold.

Sympathectomy has no lasting effect on the blood pressure of normotensive or renal hypertensive dogs, although the blood pressure of neurogenic hypertensive animals is lowered. This does not preclude the possibility that this procedure may be of value in essential hypertension since the similarities between experimental renal hypertension and essential hypertension do not necessarily mean even a partial common pathogenesis. Although sympathectomy has no lasting effect on the blood pressure of normotensive humans, there might conceivably be a difference between normotension and essential hypertension in this respect. A critical examination of the results reported for partial and complete sympathectomy, however, leads to less optimistic conclusions than some of the authors draw. Some authorities even question whether there is a significant effect from sympathectomy in essential hypertension and ascribe any improvement to psychotherapy, altered living regimen, and the nonspecific effect of the operative procedure. However, a minority of essential hypertensives, variously estimated at 10 to 20 per cent, do obtain what appears tantamount to a cure. Unfortunately, the methods of preoperative study presently available are not too satisfactory in differentiating patients who will obtain an excellent result from sympathectomy. This group may ultimately be segregated from the genus, essential hypertension, as having an elevated pressure primarily on a neurogenic basis. Whether the long range outlook for the majority of essential hypertensives subjected to sympathectomy is materially altered by the procedure is presently unanswered. Sympathectomy will, of course, definitely reduce the pressor component of emotional states and other forms of stress.

### SUMMARY

Essential hypertension is fundamentally due to slight generalized arteriolar vasoconstriction of the systemic circulation, with compensatory increased force of cardiac contraction. The fundamental pathogenesis of this vasoconstriction is not yet established. Increased tone of the vasomotor system, a renal pressor effect, or an altered anterior pituitary-adrenal cortex relationship may be involved. Within the genus, essential hypertension, there may be three or more species of hypertension corresponding to these mechanisms and others presently unknown. Cortico-hypothalamic imbalance may exert an effect through any of these three mechanisms and unquestionably this

# CASE REPORTS

---

## POLYCYSTIC DISEASE OF THE LIVER; REPORT OF TWO CASES DIAGNOSED BY PERITONEOSCOPY \*

By DAVID NIEMETZ, M.D., ARCHER SOKOL, M.D., and LESTER MEISTER, M.D.,  
*Beverly Hills, California*

A REVIEW of the available literature <sup>1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11</sup> of the past 10 years with reference to this uncommon anomaly, in its isolated form or in association with cystic disease of other organs, indicates that its diagnosis in the reported cases has been established at autopsy or by recourse to laparotomy. This report is presented to illustrate the diagnosis by means of peritoneoscopy.

### CASE REPORTS

*Case 1.* A Mexican female, 68 years of age, entered the Los Angeles County General Hospital July 25, 1946, complaining of loss of appetite, increasing fatigue, and weight loss of 10 pounds during the preceding four weeks. She had been referred to the hospital by a physician because of the foregoing complaints. Associated were symptoms suggestive of active pulmonary tuberculosis, consisting of occasional night-sweats and expectoration of blood-streaked sputum. She also complained of vague, right upper abdominal distress, occurring after eating fatty foods. Her lack of appetite was attributed to heartburn. On physical examination, her temperature was 99.4° F. (37.4° C.), pulse 80, and respirations numbered 20. The blood pressure was 150 mm. Hg systolic and 80 mm. diastolic. Examination of the chest showed a slight degree of supraclavicular wasting bilaterally. Harsh bronchovesicular breath sounds and fine râles were heard at both apical areas. The liver edge was palpated 9 cm. below the right costal margin at the midclavicular line. It was fairly sharp, non-tender, and extended across the abdomen to the opposite costal margin. The surface and the edge exhibited irregular nodularity. The lower pole of the left kidney was readily palpable, but was not fixed or otherwise remarkable. A small, reducible, soft, non-tender mass was discovered in the right inguinal area. The remainder of the physical examination was normal. Laboratory studies were as follows: Hemoglobin 58 per cent (9.9 gm.), erythrocytes 2.9 million, leukocytes 7,500, with a normal differential count. Urine (catheterized specimen) showed: specific gravity 1.012; pH 5.0; sugar 0, albumin 0; microscopic: 10 leukocytes per high power field, without erythrocytes or casts. Stool specimens (two) were negative for occult blood. Kahn reaction was negative, and the Wassermann reaction was positive on two occasions. (Roentgenographic examinations showed metallic deposits in the buttocks.) A barium enema showed no abnormality of the colon. However, the liver was noted to have an unusually broadened, rounded lower margin. Barium examination of the upper gastrointestinal tract revealed the stomach to be displaced ventrally. A postero-anterior film of the chest showed evidence of bilateral apical fibrotic and exudative tuberculosis. Three 24-hour sputum concentrates were negative for acid-fast organisms.

\* Received for publication June 10, 1947. From the Departments of Medicine, University of Southern California and College of Medical Evangelists, at the Los Angeles County General Hospital.

normal limits. The bromsulfalein excretion test (dose of 5 milligrams/kilogram) showed 29 per cent of dye retained after 45 minutes. Serum alkaline phosphatase was 6.6 Bodansky units. An oral glucose tolerance test with 100 grams of glucose showed the following blood sugar values in milligrams per 100 cubic centimeters Folin-Wu: Fasting, 99; 15 minutes, 108; 30 minutes, 129; 45 minutes, 146; 60 minutes, 180; 120 minutes, 210. Urine diastase excretion was less than 1,000 units (normal). The non-protein nitrogen of the blood was 35 milligrams per 100 cubic centimeters. Serum inorganic phosphorus was 3.8 milligrams per 100 cubic centimeters. A modified Mosenthal test showed a normal range of specific gravity. The fractional phenol-sulfonephthalein excretion was also normal. Excretory and retrograde urography were done, revealing no radiologic evidence of renal polycystic disease. The right kidney appeared to be displaced downward by the enlarged liver, and the left kidney was also low in position. Both renal pelves were moderately rotated.

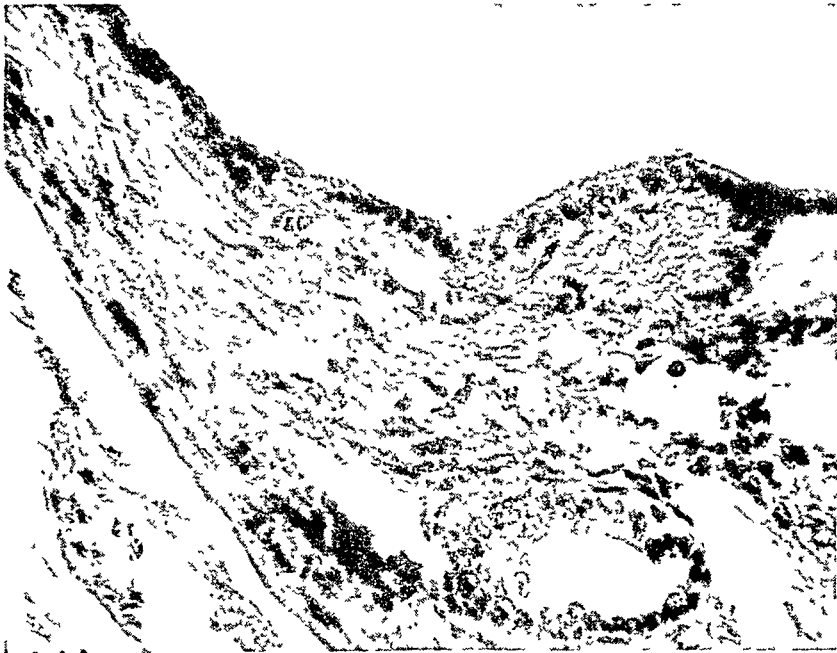


FIG. 2. Cystic areas in liver. Hematoxylin and eosin.  $\times 500$ .

The patient's presenting symptoms disappeared within a few days following entry in July. On September 17, 1946 an incarceration of the right indirect inguinal hernia occurred. This was relieved by appropriate surgical means, with a normal convalescence. The hemogram became normal prior to the patient's discharge from the hospital, at which time she was referred to the chest and gastroenterology clinics.

*Case 2.* E. B., a 48 year old Negress, was admitted November 20, 1947 with complaints of abdominal tenderness and intermittent pain throughout the abdomen for nine years. During this time she never had felt well. Occasional tarry stools were noted during the past year. Anorexia, nausea, and vomiting were present for two days prior to entry.

Past history included the usual childhood diseases, typhoid fever, and fever diagnosed without blood smears as "malaria" when a child. At the age of 28 an unspecified type of abdominal tumor had been removed via a lower midline incision. A chronic conjunctivitis and rare, transient yellowing of the sclerae had been present for nine years. One year before admission evanescent swelling of feet and ankles

Here the cysts ranged from a few millimeters to larger, up to one centimeter in diameter. Diagnosis: Polycystic liver disease.

Course following peritoneoscopy: Severe ileus developed, and continual suction via Levine tube was applied. After seven days this was discontinued and soft diet commenced. The patient was released one week later, on March 13, 1948, with some right upper quadrant tenderness still present. She was referred to the Outpatient Department for further investigation as to the presence of cystic involvement of kidneys and pancreas, which was not evident, however, in her clinical findings in the hospital.

### COMMENT

1. The finding of definite functional impairment of the liver is not surprising in case 1, since the degree of involvement of the liver parenchyma was extreme. The fact that liver function was not more disturbed can be attributed to the very slow progress of the condition.

2. Of 499 cases of cystic disease of the liver of all types reported by Davis,<sup>1</sup> 152 had cystic disease of the kidneys. Detailed studies in case 1 showed no evidence of this association, nor was evidence obtained establishing pancreatic involvement.

3. The microscopic findings present in case 1 are consistent with those described by Wooten<sup>6</sup> in congenital anomalies of this type.

4. In case 1 peritoneoscopy was instrumental in revealing a relatively benign process where malignant disease of the liver was suspected.

5. Case 2 confirms the impression that the appropriate diagnosis in this condition can be offered clinically and safely confirmed by peritoneoscopy. Liver aspiration biopsy appears to offer inadequate information and may be misleading if fluid is obtained resembling that seen in amebic abscess of the liver.

### SUMMARY

1. Two cases of polycystic disease of the liver, diagnosed by peritoneoscopy, are presented, with illustrations of the microscopic pathology in one.

2. Impaired liver function was demonstrated in these cases.

3. Evidence of cystic disease of the other organs was sought with negative results.

### BIBLIOGRAPHY

1. DAVIS, C. R.: Nonparasitic cysts of the liver, *Am. Jr. Surg.*, 1937, xxxv, 590.
2. BRADSHAW, T. E.: Polycystic disease of the liver, *Irish Jr. Med. Sci.*, 1938, Series vi, 768.
3. ALBRITTAİN, J. W., and CORNBROOKS, E. I.: Polycystic disease, *Bull. School Med. Univ. Maryland*, 1939, xxiv, 121.
4. INLOW, W. D., and RICHARD, N. F.: Polycystic disease of the liver, *Jr. Indiana State Med. Assoc.*, 1942, xxxv, 4.
5. MITCHELL, T.: Cystic liver of the newborn, case report, *Memphis Med. Jr.*, 1942, xvii, 163.
6. WOOTEN, S. F.: Pathogenesis of congenital anomalies of the intrahepatic and extrahepatic bile ducts, *N. Y. State Jr. Med.*, 1943, xliii, 727.
7. WILLIS, R. A.: Carcinoma arising in congenital cysts of the liver, *Jr. Path. and Bact.*, 1943, lv, 492.

illness had started six days previously when the patient was seized with a severe attack of upper abdominal pain and profuse vomiting, first of ingested food and then of a bile-stained mucoid material which contained streaks of blood. On the following day the temperature rose to 102° F. There was a tarry stool, and the pain became localized in the left upper quadrant. Under conservative management the intensity of the pain diminished, the temperature receded, and the vomiting ceased. The patient was admitted for observation and study.

The past history disclosed the following. Fourteen years preceding admission the patient noticed the appearance of nodular swellings on his forearms and hands and had difficulty in flexing his fingers. Biopsy disclosed Kaposi sarcoma. Under roentgen-ray treatment these swellings disappeared. They recurred four months later. There was no pain nor other sensory disturbance. Crops of these lesions recurred periodically on the upper extremities. These responded at all times to radiation therapy. In 1940 some of the lesions on the right forearm became ulcerated. At about this time lesions were observed on the feet and subsequently on the legs. Some of these also broke down. The ulcerated lesions discharged a purulent material and then healed, leaving dry, brown scaly areas. In 1943 ulcerations on the right forearm appeared which failed to heal and extended despite therapy. An amputation of the right arm at the mid-humerus was performed at Memorial Hospital. The amputated member was described as "a seething mass of multinodular ulcerating and necrotic Kaposi's disease. Tumor nodules varied from a few mm. to 2 cm. in diameter. The larger masses were necrotic and foul-smelling. The entire extremity was edematous. There was no tumor in the lymph nodes accompanying the specimen." Following the amputation only occasional, isolated nodules appeared in the skin. These were surgically excised, the most recent one on the left thigh about four weeks before admission.

About one year prior to the present illness the patient began to experience attacks of dull, generalized abdominal cramps and nausea. The cramps lasted only a few minutes, recurred frequently during the day and night and were neither related to nor relieved by food. The attacks increased in frequency and severity, and about two months before admission the patient began to vomit after meals. The vomitus was bile-stained and contained ingested food but no blood. He was placed on ulcer treatment without relief. There had been a weight loss of about 35 pounds in the past year.

Physical examination disclosed the following. The eyes, ears, nasal and oral cavities were negative. The neck showed no adenopathy. The heart and lungs were negative. The blood pressure was 110 mm. Hg systolic and 90 mm. diastolic. There were moderate tenderness, spasticity and an indefinite mass the size of an orange in the left upper quadrant. Rebound tenderness was present. The liver and spleen were not palpable. Rectal examination was negative. There was a well healed amputation stump at the level of the right mid-humerus. A number of enlarged firm lymph nodes were present in the right axilla, the largest being the size of a walnut. Throughout the skin, but most marked on the extremities, were numerous flat pigmented areas. The skin over the legs and feet was dry and scaly.

The temperature was normal, the pulse rate slightly increased. The blood count showed a hemoglobin of 54 per cent, and 2,960,000 red blood cells. Differential smear showed 84 per cent polymorphonuclear cells, 6 staff cells and 10 lymphocytes. The sedimentation rate was 17 minutes for 18 mm. The urine showed a faint trace of albumin and an occasional red blood cell. Occult blood was present in the stool.

*Course.* The patient continued to improve during the first three hospital days. The temperature remained normal. The pain completely subsided. The abdomen became soft, the suggestive mass disappeared, and the tenderness in the left upper quadrant was minimal. On the fourth day, while straining during defecation, the

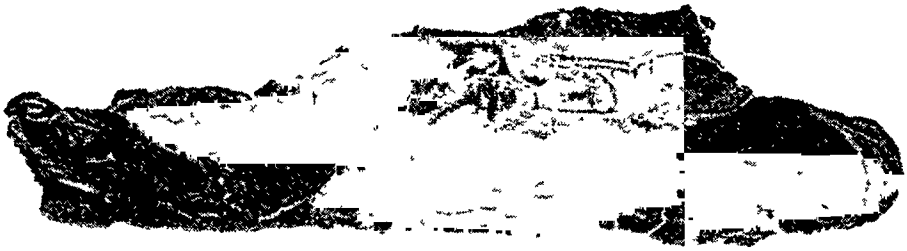


FIG. 2. A sagittal section through the jejunum reveals the hemorrhagic mass infiltrating its wall.

mass which was well demarcated from the surrounding intestinal wall (figure 2). No other foci of tumor tissue were present in the gastrointestinal tract.

The large right axillary mass was composed of discrete lymph nodes, the largest measuring 4 cm. in diameter (figure 3). The architecture of the nodes was replaced by soft gray opaque tumor tissue marked by focal hemorrhage and necrosis. No active skin lesion either grossly or microscopically, was found. Small accumulations of hemosiderin laden phagocytes were noted in a dermis that was densely fibrotic. Careful examination of the other viscera revealed no metastatic foci.

*Microscopic Description.* Sections from the base of the jejunal ulcer revealed a malignant spindle cell tumor showing definite vasoformative tendencies (figure 4). The individual tumor cells were spindle shaped with oval to rounded vesicular nuclei. Hyperchromatism and cellular pleomorphism were evident. A moderate number of mitotic figures was seen. The tumor tissue extended through the entire thickness of the jejunal wall, and the edges of the grossly described fistula were lined by neoplastic tissue which was partially necrotic and acutely and chronically inflamed. The



FIG. 3. The enlarged right axillary nodes show focal necrosis and hemorrhage in the metastatic tumor tissue.

that the jejunal tumor had its origin in the blood vessels of the intestinal wall. Despite the foregoing arguments, it must be conceded that the axillary lymph node involvement does actually constitute metastasis from neoplastic tissue previously present in the right upper extremity.

### SUMMARY

1. A case of Kaposi's sarcoma of 14 years' duration has been presented. In addition to the skin manifestations, the jejunum and axillary lymph nodes were also involved.

2. Perforation of the jejunal tumor caused generalized peritonitis and death. Such a complication has not been described heretofore.

3. Pathologic studies suggest that the jejunal sarcoma constitutes a site of origin independent of the skin involvement.

### BIBLIOGRAPHY

1. STATS, D.: The visceral manifestations of Kaposi's sarcoma, Jr. Mt. Sinai Hosp., 1946, xii, 971-983.
2. NESBITT, S., MARK, P. F., and ZIMMERMAN, H. M.: Disseminated idiopathic hemorrhagic sarcoma (Kaposi's disease); report of case with necropsy findings, *Ann. Int. Med.*, 1945, xxii, 601-605.
3. AEGERTER, E. E., and PEALE, A. R.: Kaposi's sarcoma; a critical survey, *Arch. Path.*, 1942, xxxiv, 413-422.
4. TEDESCHI, C. G., FOLSOM, H. F., and CARNICELLI, T. J.: Visceral Kaposi's disease, *Arch. Path.*, 1947, xliii, 335-357.
5. WILLIS, R. A.: The spread of tumors in the human body, 1934, J. & A. Churchill, London.

---

## A CASE OF MESENTERIC VENOUS THROMBOSIS WITH SURVIVAL \*

By ALLAN M. GOLDMAN, M.D., F.A.C.P., and JAMES D. RIVES, M.D.,  
*New Orleans, Louisiana*

THIS case is presented in the hope of contributing something of value to the literature on vascular accidents. From the history obtained it was difficult to estimate how long the mesenteric thrombosis had been present when the patient was first seen. The history was superficial owing to the condition of the patient and the inability of his wife to confirm the sequence of events.

### CASE REPORT

The chief complaint was generalized, knife-like abdominal pain, radiating through to the back and most severe in the right lower quadrant. The patient, a 48 year old white male in the automotive accessory business, stated he had been having watery diarrhea for the preceding three weeks with occasional episodes of nausea and vomiting. Cramping abdominal pain was intermittent and no blood was noted in the

\* Received for publication May 14, 1947.

From the Departments of Medicine and Surgery of the Touro Infirmary, New Orleans, La. (Presented at the Monthly Staff Meeting, March 12, 1947.)

in the small intestine, but the absence of any distention was against a diagnosis of intestinal obstruction. The properitoneal fat lines were noted, but indistinct, suggesting that there might be some fluid in the peritoneal cavity. However, the psoas muscle shadows were sharp, ruling out any hemorrhage in the retroperitoneal space. The presence of fluid levels in the small intestine brought up the question of mesenteric thrombosis, but the findings were not characteristic and a diagnosis would require correlation with clinical and other laboratory findings.

Electrocardiogram on admission revealed a sinus tachycardia, rate 150, with depression of the ST segment in Lead II. It was otherwise non-contributory. He was given 2,000 c.c. of glucose and 500 c.c. of blood by vein, at which time his blood pressure rose to 160 mm. Hg systolic and 100 mm. diastolic, and the pulse slowed to 110. A Levine tube, with continuous suction, was maintained from the time of admission. By 7:00 p.m., approximately five hours after admission, it was decided to take the patient to surgery.

Laparotomy was performed by one of us, J. D. R., and a massive venous mesenteric thrombosis was noted. There was no apparent cause for this accident. Approximately 11 feet of gangrenous small intestine with a margin of normal bowel was resected. An aseptic end to end anastomosis was performed and more than one liter of serosanguineous fluid removed from the peritoneal cavity. An additional 500 c.c. of blood were given in the operating room. The patient left the table in fairly good condition. Continuous oxygen was administered on return to his room and heparin therapy was begun by the intravenous route. The clotting time varied for the next few days between six and 28 minutes.

On February 3 the following blood chemistry was noted. Non-protein-nitrogen, 50; dextrose, 97; sodium chloride 471; prothrombin power, 10 per cent. Vitamin K, 10 mg., was given because of the low prothrombin. Fluid, electrolyte, protein and vitamin balance were maintained by the use of glucose and saline, intravenous amigen solution, blood transfusions, and large doses of parenteral vitamins daily. The blood type was AB, Rh positive. At no time during the first postoperative week did the temperature exceed 100.4° F. by rectum. On February 4 the icterus index was 100; Van den Bergh test gave a biphasic direct reaction; the cephalin flocculation was 2 plus; the prothrombin power was 68 per cent; non-protein nitrogen was 33, and the urinalysis revealed 35 to 40 red cells per high power field. The red cell count was 4,750,000 and the white blood count, 15,700, with 82 polymorphonuclears. The next day the icterus index was 120, and three urine examinations were negative for blood cells. Because of the progressive jaundice and the general condition of the patient it was decided to discontinue heparin therapy. A non-protein nitrogen taken at this time was 31. By February 7 the icterus index had dropped to 100; the serum proteins totaled 5.07 with 3.01 albumin and 2.06 globulin.

Because of marked abdominal distention and a continuing ileus the Levine tube was replaced by a Miller-Abbott tube which was advanced with the aid of a bedside roentgen-ray unit. Reports were as follows February 8, 1947: Examination of the abdomen with the bedside unit indicated that a Miller-Abbott tube had entered the proximal jejunum, which apparently lay in the right upper quadrant of the abdomen. Very little gas was seen in the stomach and in scattered small intestinal loops. The colon exhibited a normal quantity of gas in the descending portion and rectum. It was assumed that the abdominal distention was due in large measure to a collection of fluid. The possibility that the fluid might be within the intestine as well as in the peritoneal cavity could not be ruled out.

The general condition of the patient remained good except for the persistent ileus. Blood pressure readings ranged from 140 to 160 mm. Hg systolic and from 90 to 110 mm. diastolic. The pulse rate ranged from 88 to 120, but was consistently around 90. On February 10, 1947 the following roentgenographic report was rendered: Re-



cal), such as a kink, or whether it was due to atony. At this time the white blood count was 9,600 with 80 polymorphonuclears and the red blood cells 4.4 million.

The following day the abdomen appeared much less distended, and the patient retained all liquids with the tube clamped off. On February 12 the Miller-Abbott

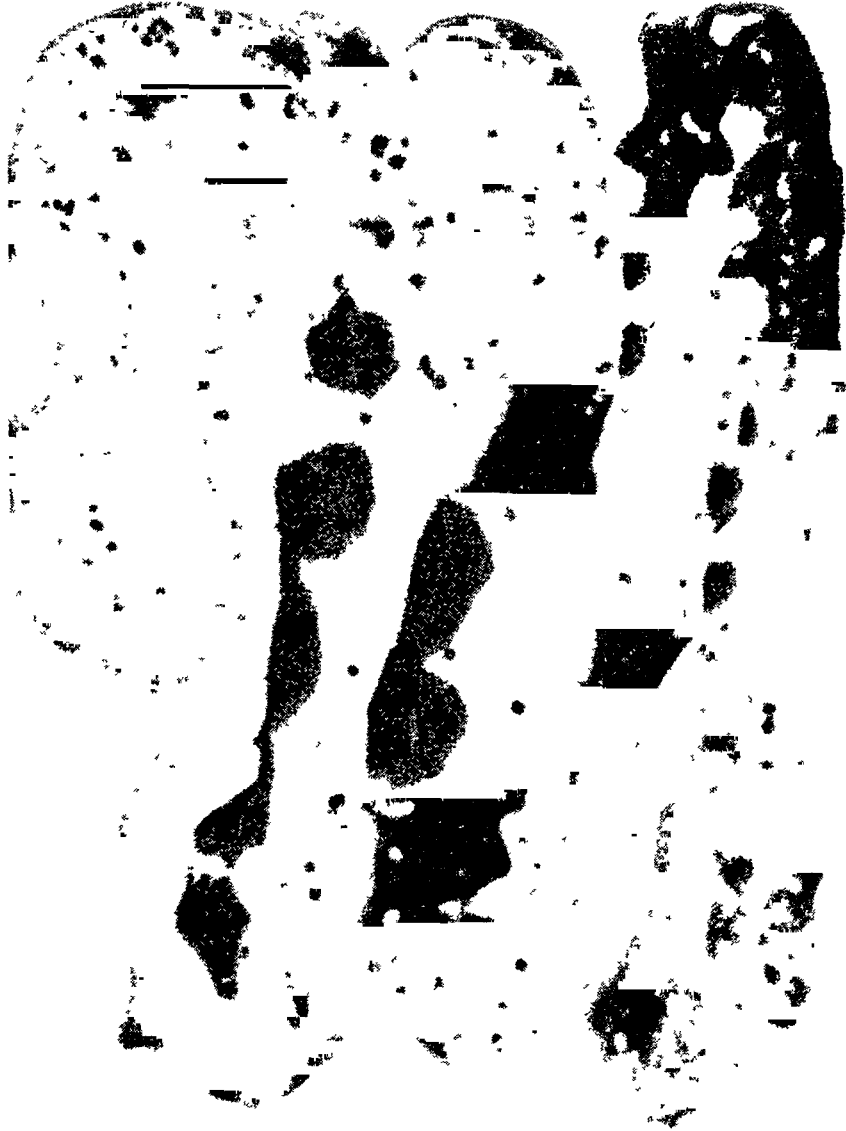


FIG. 2. Gross pathology. Section of gangrenous ileum removed at operation.

tube was removed and soft diet was begun. The icterus index at this time was 80. By February 15 he began passing liquid stools which were cultured and found to be negative for parasites. That day the icterus index was 60, but on February 17 the cephalin flocculation was 3 plus. Daily infusion and parenteral vitamin therapy were continued. At this time he was afebrile and remained so until the time of discharge.



FIG. 4a. Gastrointestinal series (see also figure 4b) taken prior to discharge from hospital.

February 24 the total serum proteins were 6.29, albumin 3.24, and globulin 2.95. Repeated stool examinations were negative for parasites and stool cultures were negative for pathogens.

There was no delay in wound healing but the patient continued to have cramping abdominal pain with alternating liquid and solid stools, three to five a day. Opium suppositories and Kaopectate-Opium mixtures were used with marked relief of symptoms. Frequent small feedings were taken, and the bowel seemed gradually to adjust to the disturbed physiology. On February 26, 1947 he was ambulatory and a gastrointestinal series was taken, with the following results: Fluoroscopic examination of the chest revealed no abnormalities. The contrast meal traversed the esophagus without difficulty. The stomach was of a J type and was displaced toward the midline by a

bowel and colon, with the head of the column in the transverse. Fluoroscopy indicated that the terminal ileum and cecum were normal in contour and not unduly tender. The mobility of the cecum was somewhat limited.

The patient continued to improve from day to day, and the irritability of the bowel gradually subsided. Stools at times were well formed and on alternate occasions were liquid brown with no gross blood. The average number per day was three or four. The appetite was good, but at times the patient complained of mild abdominal cramping pain. Further examination in the form of proctoscopic study and barium enema had to be deferred because of the refusal of the patient to stay in the hospital. At the time of discharge March 2, 1947, moderate splenomegaly persisted, and the liver was enlarged 3 cm. below the costal margin. He was afebrile during the last two weeks' stay in the hospital.

Report of the pathologist was as follows: The specimen consisted of 435 cm. of small intestine (11.1 ft.), 255 cm. of which was gangrenous. The affected portion of this specimen was soft, thick walled, edematous and black in appearance. Thrombi were noticeable in the mesenteric vessels. The unaffected portion was dusty colored, somewhat edematous and grayish pink. The intestine was opened throughout its entire length and the mucosa of the affected portion was smooth and the lumen engorged with blood. Many of the small arterioles and venous capillaries presented necrotizing inflammatory reaction. It was not possible to determine whether this was primary or secondary. The larger vessels appeared patent. The conclusion was: Infarcted small bowel with gangrene, cause undetermined.

Subsequent follow-up of the patient at home during the month of March revealed him to be comfortable and ambulatory. The number of stools passed each day was reduced to a maximum of three. On March 11 sigmoidoscopic examination revealed a normal mucous membrane, and culture, zinc flotation, and direct smear examinations were negative for pathogens. By the end of March the spleen was barely palpable and the liver noted only on inspiration. He had gained five pounds and appeared to have completely recovered from the abdominal vascular accident.

A brief review of the literature reveals that mesenteric thrombosis is extremely rare in children, occurring most commonly in adults between the ages of 30 and 70 years. Males predominate over females, with the highest incidence in the fourth decade. At the Mayo Clinic up to 1938, Whittaker and Pemberton<sup>10</sup> report 60 cases, of which 57 came to necropsy. In 60 per cent of these the mesenteric vascular occlusion was unrelated to previous surgical procedure. The remaining followed operative procedures such as splenectomy, biliary or pancreatic procedures, appendectomy, or drainage of a gangrenous ruptured appendix, gastroduodenal operations, herniorrhaphy, operations on the transverse colon.

Superior mesenteric arterial occlusion was most common. Thrombosis was found following operation where conditions such as arteriosclerosis and splenic anemia existed. Embolus was associated with degenerative heart disease or with valvular disease. Lowance and Jones<sup>7</sup> report a case of mesenteric thrombosis in the presence of subacute bacterial endocarditis. Occlusion of the superior mesenteric vein occurs secondary to ascending thrombosis attributed to an infectious process such as appendicitis and pelvic infection. It also occurs secondary to descending thrombosis from the portal vein, with hepatic disease, or following abdominal surgical exploration.

In the series of Whittaker and Pemberton<sup>10</sup> a review of the pathology revealed vascular occlusion to be complete in each case studied. Thirty per cent of the cases had an associated thrombosis of the portal vein and 11.6 per cent

Further search as to the cause of the idiopathic venous thrombosis is being carried out.

## BIBLIOGRAPHY

1. ALLEN, E. W., BARKER, N. W., and WAUGH, J. M.: A preparation from spoiled sweet clover, Jr. Am. Med. Assoc., 1942, cxx, 1009.
2. Case Report: Thrombosis of the mesenteric veins in chronic myelogenous leukemia, New Eng. Jr. Med., 1945, ccxxxiii, 604.
3. D'ABREU, F., and HUMBLE, J. G.: Mesenteric venous thrombosis, Lancet, 1946, i, 534.
4. DORAN, W. T., and DORAN, W. T., JR.: Mesenteric thrombosis of the terminal ileum, Am. Jr. Surg., 1944, lxxiii, 146.
5. DYE, W. J. P.: Mesenteric thrombosis, New Eng. Jr. Med., 1935, ccxii, 105.
6. FOX, P. F.: Mesenteric thrombosis with postoperative administration of Dicumarol, Illinois Med. Jr., 1944, lxxxvi, 314.
7. LOWANCE, M. J., and JONES, E. C.: Subacute bacterial endocarditis, *Streptococcus viridans*, with mesenteric thrombosis and recovery, Ann. Int. Med., 1946, xxiv, 485.
8. WANGENSTEEN, O.: Intestinal obstruction due to mesenteric thrombosis and embolism, Christopher Textbook of Surgery, 4th Ed., 1945, W. B. Saunders Co., Philadelphia, 1057.
9. WARREN, SHIELDS, and EBERHARD, T. P.: Mesenteric venous thrombosis, Surg., Gynec. and Obst., 1935, lxi, 102.
10. WHITTAKER, L. D., and PEMBERTON, J.: Mesenteric vascular occlusion, Jr. Am. Med. Assoc., 1938, cxi, 21.

---

ENDOCARDITIS CAUSED BY ORGANISM MORPHOLOGICALLY AND CULTURALLY IDENTIFIED AS  
*C. diphtheriae*\*

By BERTRAM ZHEUTLIN, M.D., *Ann Arbor, Michigan*

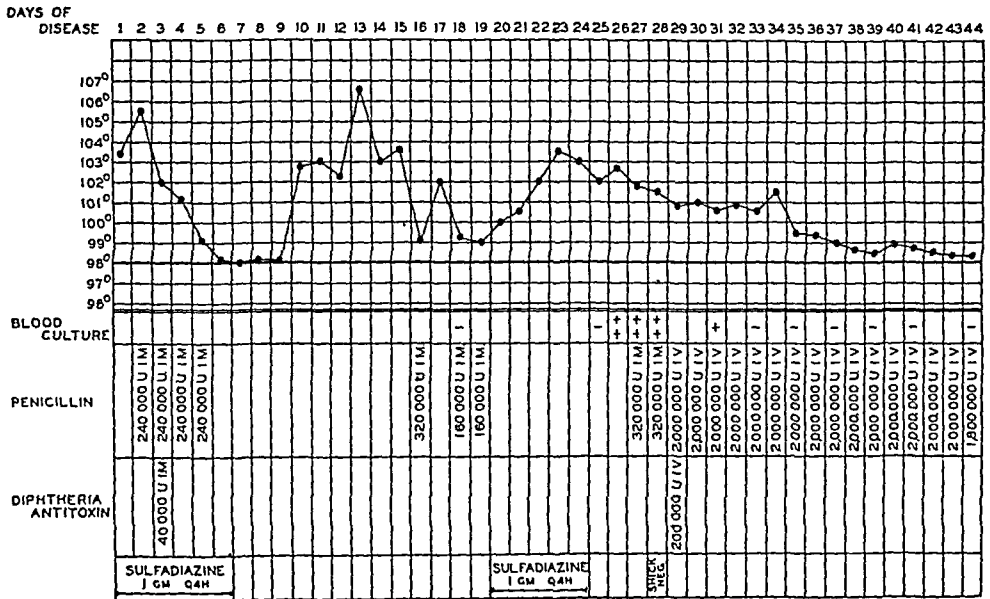
*Corynebacterium diphtheriae* characteristically affects the heart by producing a toxin which causes a myocarditis. Only in unique cases does the diphtheria organism directly affect the pericardium or endocardium. This report deals with a case in which endocarditis was caused by an organism resembling the Klebs-Loeffler bacillus morphologically and culturally, and which proved to be virulent for guinea pigs.

## CASE REPORT

A 19-year-old white enlisted man was admitted to the hospital May 26, 1946, with the chief complaints of sore throat, chilly sensations, and fever. The family history was non-contributory. The past history revealed that the patient had had good general health and strength until eight years before induction into the Army. The patient stated that in 1936 he had rheumatic fever followed by St. Vitus dance, following which he spent much of the last eight years in medical institutions. He had had the usual childhood diseases but no other significant infectious diseases. He did not know if he had had diphtheria immunization when a child, and he was not immunized against diphtheria while in the Army. The rest of the past history was not significant.

\* Received for publication March 5, 1947.

murmur which was transmitted to the axilla and which was not affected by change in position and respiration. There was an early, short, harsh systolic murmur in the pulmonic area which varied with position and was not transmitted into the neck vessels. The second pulmonic sound was accentuated. A diastolic third heart sound could be heard at the apex when the patient was supine but disappeared when the patient rotated to either side. Over both ankles there was tenderness, heat, swelling, and redness. There were numerous petechiae over these latter areas. There was no lymph node enlargement and the spleen was not palpable. However, there was tenderness to palpation in the left upper abdominal quadrant. The rest of the physical examination revealed no pertinent abnormalities.



Sulfadiazine was discontinued, and the next day, the twenty-fifth hospital day, blood cultures were drawn at a time when the temperature was thought to be rising. During the next four days seven blood cultures were made, each one producing a heavy growth of pleomorphic gram positive bacilli, morphologically and culturally resembling *C. diphtheriae*. The organisms were cultured from the blood in the following manner: Three cubic centimeters of blood were put into brain heart infusion and para-aminobenzoic acid, 0.1 per cent, a medium prepared by Difco. The culture was observed for seven days and any growth noted during this time was subcultured to a blood plate. The organism grown in the brain heart infusion was a pleomorphic gram-positive rod resembling *C. diphtheriae* morphologically, and from the blood plate was transferred to Mueller's serum tellurite where colonies typical for the Klebs-Loeffler bacilli were produced. This type of medium inhibits the growth of cocci and diphtheroids and on it *C. diphtheriae* produces a characteristic colony distinguishable from *C. xerosis* and *C. Hoffmani*. Sugar fermentation tests identified the organism as belonging to the mitis strain.

To test the virulence of the organism after it was identified as *C. diphtheriae*, it was grown on brain heart infusion for 24 hours and a saline suspension containing approximately 900,000 organisms per cubic centimeter was made. One-tenth centimeter of this suspension was injected subcutaneously into a shaved area on the abdomen of a guinea pig. Three hours later 1,000 units of diphtheria antitoxin were administered intraperitoneally, and at another shaved area 0.1 c.c. of the saline suspension containing about 90,000 organisms was injected subcutaneously as a control.

During the patient's entire hospital stay, the red blood count ranged between 4.5 and 5 million, with the hemoglobin always above 90 per cent. The white cell count ranged between 10,000 and 14,000 with a normal differential. Repeated throat cultures and urinalysis never revealed any significant abnormalities. The Schick test, repeated several times, was negative.

At the time of writing the patient had not had penicillin for six weeks and had been out of bed for four weeks. Blood cultures had been sterile. The patient had been afebrile and there had been no evidence of embolic phenomena. The loud apical systolic murmur remained present and the third heart sound was heard while in the supine position but, as before, disappeared when the patient rolled to either side. It must be remembered that these cardiac findings were not present at the time of admission. The blood count and urinalysis were within normal limits. Subjectively the patient's condition was excellent, his appetite enormous, and he was rapidly regaining the weight he had lost. The patient was returned to the Zone of Interior, so further personal follow-up was not possible.

#### SUMMARY

A case of endocarditis caused by an organism identified as *C. diphtheriae* is reported because of the extreme rarity with which the Klebs-Loeffler bacillus directly attacks the endocardium.

---

### FATAL MERCURIALISM DUE TO PROLONGED INTRAVENOUS ADMINISTRATION OF A MERCURIAL DIURETIC \*

By MAURICE B. SIEGEL, M.D., and ALAN J. FRIEDMAN, M.D.,  
*Los Angeles, California*

THE clinical use of organic mercurials to control the edema of congestive heart failure has had widespread clinical application since their introduction a generation ago.<sup>1, 2, 3</sup> These diuretics have had considerable usage also in the control of edema in the chronic nephritides,<sup>3, 4</sup> although some point out that their use should be contraindicated because of their nephrotoxic effects.<sup>5, 6</sup> In the case to be presented, mercupurin was used over a period of several months in doses ranging up to 4 c.c. twice weekly to control the edema of a young diabetic man with the syndrome of Kimmelstiel-Wilson.<sup>7</sup> The postmortem examination revealed changes in the kidneys and gastrointestinal tract which were definitely consistent with mercury poisoning and quantitative chemical examination disclosed a toxic amount of mercury in the involved organs.

#### CASE REPORT

This 23 year old white male was first seen in the outpatient department of this hospital in 1937 for the treatment of his diabetes which had been present for the past 12 years. During this interim, the patient had been treated with insulin and diet.

\* Received for publication May 5, 1947.

From the Division of Pathology, Cedars of Lebanon Hospital, Los Angeles, California.

blood cells per high power field. At this time, in addition to the diabetic régime, low salt diet, bed rest, and restricted fluids, mercupurin in doses of 2.2 c.c. twice a week was instituted for the relief of the edema which was now extensive and interfered with his activity. This therapy was continued later in the outpatient department of this hospital and on subsequent hospital admissions for the remainder of his life. His edema persisted in spite of this therapy, and in the later months of his life he required larger doses (4.4 c.c. twice a week) intravenously in order to obtain effective diuresis.



FIG. 1. ( $\times 60$ ). Section of large bowel showing necrosis of mucosa with surface slough and polymorphonuclear infiltration.

On July 26, 1946, the patient was readmitted with anorexia, vomiting and persistent bloody diarrhea. There was now persistent anasarca despite the use of mercurial diuretics. Stool and blood cultures were negative. Blood pressure was 180 mm. Hg systolic and 120 mm. diastolic, non-protein nitrogen was 86 mg. per cent, creatinine 4.3 mg. per cent, serum albumin 2.4 gm. per cent, serum globulin 2.5 gm. per cent, and hemoglobin 63 per cent. The patient was given several blood transfusions and was discharged unimproved for follow-up care and further therapy in the outpatient department.

and showed considerable acute passive hyperemia. The kidneys each weighed 180 grams, which is somewhat heavier than normal. The external surfaces were smooth and pale. On section, the cortex was moderately thickened and the cortical striations were obscured. The blood vessels were not unduly prominent. The gastrointestinal tract was moderately distended with gas and hemorrhagic, semifluid fecal material. The wall of the large bowel was moderately thickened. The mucosa showed extensive ulcerations with considerable hemorrhagic discoloration. The pancreas was located with considerable difficulty. It was represented by small isolated masses of tan tissue



FIG. 3. ( $\times 675$ ). Section showing mitotic figure in regenerating tubule.

having the usual lobular architecture of pancreatic tissue. The total amount was estimated to weigh not more than 25 grams. The posterior halves of both eyes were removed for examination. The vitreous chamber contained irregular masses of semi-translucent and opaque grayish-white tissue. The normal structures were almost completely obliterated. The retina could not be identified. The choroid coat and the sclera showed nothing remarkable grossly. The other organs, including the brain, revealed no significant findings.



arteries also showed a considerable amount of sclerosis with medial and intimal thickening.

Microscopic examination of the eyes revealed a considerable distortion of the retina, with varying stages of degenerative change. There was considerable organizing blood clot in the vitreous chamber. The outer coats of the eye revealed nothing remarkable.

Because the hemorrhagic ulcerative colitis was too extensive to be adequately explained by the degree of azotemia, the possibility of mercurialism was suspected. Portions of the colon, stomach, kidneys and liver were subjected to toxicological examination.

The analysis for mercury was made by Dr. D. G. Simonson (Los Angeles County General Hospital). The following values for mercury were secured:

Colon .....	5.3 mg. of mercury per 100 grams of tissue;
Stomach .....	4.6 mg. of mercury per 100 grams of tissue;
Kidneys .....	3.2 mg. of mercury per 100 grams of tissue;
Liver .....	3.0 mg. of mercury per 100 grams of tissue.

The final anatomic diagnoses were as follows: Hypoplasia of the pancreas (with diabetes mellitus); intercapillary glomerular sclerosis (Kimmelstiel-Wilson's disease); cardiac hypertrophy, left ventricle; chronic mercurial poisoning, secondary to mercurial diuretics. The anatomical findings were consistent with the clinical diagnosis of hypertensive cardiovascular disease with cardiac failure and uremia.

## DISCUSSION

Kimmelstiel and Wilson,<sup>7</sup> in 1936, first described a nephrotic syndrome associated with hypertension and uremia complicating the course of diabetes mellitus. This was apparently attributable to sclerosis between the capillaries and the epithelium of the glomerular tufts. Siegal and Allen<sup>8</sup> reexamined diabetic and arterial nephrosclerotic autopsy material and found the typical lesions in 33.3 per cent of diabetic kidneys, and in only 1 per cent of nephrosclerotic kidneys. Goodof<sup>9</sup> reviewed 214 cases of diabetes and found 44 per cent of his cases showed the lesions of intercapillary glomerulosclerosis. Thus these investigators felt that this entity was a separate disease syndrome clinically and pathologically. However, Bell<sup>10</sup> as well as Horn and Smetana,<sup>11</sup> has stressed the non-specificity of these lesions and declare that they cannot be made the basis for a pathological diagnosis of diabetes mellitus as they are frequently found in non-diabetics and arteriosclerotic kidneys.

This patient showed the clinical and pathological features which typify the Kimmelstiel-Wilson syndrome, and more, since the sclerosis also extended to involve the arterioles and larger arteries. He developed the hypertension, persistent albuminuria with a nephrotic picture, and the progressive azotemia with termination in uremia. Whether his rising non-protein nitrogen and creatinine, anasarca and bloody diarrhea are to be explained by the renal disease or the mercurial injury cannot be settled definitely, but since the mercury was present in toxic quantities associated with characteristic nephrotic changes, the mercury was undoubtedly a major contributing factor.

Bradley,<sup>4</sup> reviewing progress in Bright's disease, declares that mercurial diuretics are not detrimental to the kidney in the nephrotic phase and are very effective in establishing diuresis. Holman and Donnelly's experimental finding

by these authors were examples of drug idiosyncrasy or anaphylaxis since the toxic signs became evident immediately following one or two doses of the mercurial. In 1933 Rosenthal<sup>20</sup> reviewed the autopsy findings on the case of a 59 year old male who died two days after receiving his second dose of Salyrgan with a clinical picture strongly suggesting a marked drug sensitivity. Postmortem examination revealed marked hemorrhagic and inflammatory changes in the colon and changes in the kidneys suggestive of a nephrosis. Tyson<sup>21</sup> and Brown et al.<sup>22</sup> also described anaphylactic deaths following mercurials and described tissue changes essentially similar to those given above by Rosenthal.<sup>20</sup> They concluded that there was no correlation between the dosage of the mercurial and the pathologic change in the tissues. Waife and Pratt<sup>23</sup> recently reviewed a case of fatal mercurial poisoning following prolonged administration of Mercurophylline. The clinical story was that of a 35 year old white female who received Mercurophylline over a six month period for the relief of edema secondary to the congestive failure of old inactive rheumatic heart disease. Autopsy findings after a uremic death were essentially the same as those described by Rosenthal, the reportable feature of their case being the long term administration of the drug as contrasted to the quicker anaphylactoid phenomena recorded in most previous reports. Whereas the above represent immediate or delayed toxic fatal results of mercurial administrations, many reports current in the literature cite examples of safe usage of these drugs over prolonged periods of time with continued effectiveness.<sup>19</sup> Leaman cites a patient receiving 437 injections of mercupurin over a five and one-half year period, and at postmortem examination no gross or microscopic evidence of renal injury was seen.<sup>24</sup>

As noted under the autopsy findings above, the various tissue concentrations of mercury ranged from 3.0 to 5.3 mg. per 100 grams of tissue. The question might be raised as to what if any tissue concentration of mercury or evidence of kidney damage would be found in patients getting mercurials over long periods of time prior to death. The biochemist<sup>25</sup> who performed these tests has made similar mercury determinations on routine necropsy tissues of patients who were treated with mercurials but who died of postoperative myocardial infarctions or from cerebrovascular accidents and found that, if no kidney impairment was present, only minute traces of mercury could be recovered. The renal tubular lesions of focal calcifications and necrotizing nephrosis, with signs of regeneration, are rarely, if ever, seen in other types of renal disease in man. Goldblatt<sup>26</sup> considers that the latter two findings, i.e., focal calcification and regeneration of tubular epithelium are practically pathognomonic of mercurial injury to renal tubular epithelium in man.

### CONCLUSION

As far as we can determine, this is the first reported case of fatal mercurial poisoning as a result of the administration of a mercurial diuretic, with quantitative determinations of the mercury content of the body tissues directly affected by mercury. Waife and Pratt<sup>23</sup> cited in their case report only qualitative determinations of mercury in the tissues, and whether or not it was present in toxic quantity is unknown. The quantities of mercury identified in our patient's tissues (obtained by duplicate determinations) are sufficiently high to represent lethal concentrations and are comparable to those usually seen in suicidal or accidental mercury poisoning.

21. TYSON, M. C.: Danger of intravenous mercurial injections in nephrosis, *Jr. Am. Med. Assoc.*, 1941, cxvii, 998.
22. BROWN, G., and OTHERS: Deaths immediately following intravenous administration of mercupurin, *Jr. Am. Med. Assoc.*, 1942, cxix, 1004.
23. WAIFE, S. O., and PRATT, P. T.: Fatal mercurial poisoning following prolonged administration of mercurophylline, *Arch. Int. Med.*, 1946, lxxviii, 42.
24. LEAMAN, W. G., JR.: Treatment of congestive failure, *Clinics*, 1946, v, 3.
25. SIMONSEN, D. G.: Personal communication to the authors.
26. GOLDBLATT, H.: Personal communication to the authors.

have demonstrated that a proportion of attacks of acute rheumatic fever may not be preceded by clinically or culturally demonstrable streptococcal infection.<sup>6</sup>

Immunological evidence linking streptococcal infection with rheumatic fever has centered about the serologic demonstration during various phases of the disease of a variety of antibodies either to the entire bacterial cell, certain of its fractions, or various products of the organism.<sup>7</sup> The ubiquity of hemolytic streptococci and the fact that they may exist in the human host at times without producing clinical evidence of infection renders the interpretation of such immunologic findings in rheumatic fever somewhat hazardous. Much of the effort expended in this direction has been productive of either negative or inconclusive results. Thus the measurement of anti-streptococcal agglutinins showed comparable titers in a series of patients with active rheumatic fever as well as in a group of patients with acute streptococcal infections unassociated with manifestations of rheumatic fever.<sup>8</sup> Precipitin tests with the type-specific M protein and the C carbohydrate have likewise yielded inconclusive results.<sup>7</sup> Since the early thirties much interest has centered about the detection and measurement of antibodies against the streptococcal products, fibrinolysin and hemolysin (streptolysin). These studies, by and large, have also yielded results which merely emphasized again the relationship between streptococcal infection and rheumatic fever but which were more indicative of the preceding infection rather than pathognomonic of the latter.

The search for other varieties of streptococcal antibodies in the sera of patients with acute rheumatic fever still continues. Typical of recent investigations are the studies of Harris et al. on streptococcal anti-hyaluronidase.<sup>8</sup> In these studies two recent avenues of investigation show some tendency to merge. Considerable interest has been recently displayed in the subject of hyaluronic acid and its enzyme hyaluronidase.<sup>9</sup> Hyaluronic acid, a mucopolysaccharide, is believed to be an important constituent of the amorphous ground substance of connective tissue. Its presence has been demonstrated in the skin, synovial fluid, mesenchymal tumors, vitreous humor and umbilical cord. Hyaluronic acid is likewise known to be present in the capsular substance of streptococci. The term, hyaluronidase, is actually a collective one and denotes a variety of enzymes which have been obtained from divergent sources. Most Group A hemolytic streptococci produce hyaluronidase. Since the basic lesions of rheumatic fever are essentially in connective tissue, the possibility that an enzyme elaborated by streptococci may produce

<sup>6</sup> JONES, T. D., and MOTE, J. R.: The clinical importance of infection of the respiratory tract in rheumatic fever, Jr. Am. Med. Assoc., 1939, cxiii, 898.

<sup>7</sup> HARRIS, T. N.: Studies on the relation of the hemolytic streptococcus to rheumatic fever. I. Review of serologic literature, Am. Jr. Dis. Child., 1948, lxxvi, 411.

<sup>8</sup> GOLDIE, W., and GRIFFITHS, G. J.: Aetiological relation of the *Streptococcus hemolyticus* to the "rheumatic" disease, Brit. Med. Jr., 1936, ii, 755.

<sup>9</sup> MEYER, K.: The biological significance of hyaluronic acid and hyaluronidase, Physiol. Rev., 1947, xxvii, 335.

confirmed. The Wedums<sup>14</sup> demonstrated that precipitins of the same type could be found in several diseases but less frequently than in rheumatic fever.

Although the concept of auto-antibody formation as a pathogenetic mechanism in rheumatic fever remains to be confirmed, further evidence of a supporting nature may be cited. Cavelti<sup>15, 16, 17, 18</sup> has demonstrated that rabbits and rats injected with homologous kidney substance plus streptococcal substances developed antibodies to plain kidney of their own species. In the rats it was found that as a result of the procedure inflammatory lesions resembling glomerulo-nephritis were produced. In further experiments Cavelti injected rats with streptococci plus extracts of rat heart, rat skeletal muscle and rat connective tissue. These animals developed antibodies to the respective tissues and were found on histological examination to have developed lesions of the valves and other connective tissue structures of the heart resembling "in a broad sense" those of rheumatic fever. In additional studies of rats focally infected with Group A hemolytic streptococci, autogenous tissue antigens appeared to be released into the blood stream during the height of infection and subsequently auto-antibodies to rat tissue were found. Carrying this work over to humans, Cavelti<sup>19</sup> prepared an antigen consisting of saline extract of normal human heart adsorbed upon collodion particles. The sera of 47 of 67 patients with active rheumatic fever produced agglutination of this antigen. Twelve normal persons displayed no antibodies and in a group of 84 patients with other diseases 1 weak and 3 doubtful positive reactions were obtained. Cavelti was unable to repeat these results in subsequent studies.<sup>20</sup> Repetition of these studies, perhaps by other immunologic technics, seems desirable.

Rich<sup>21</sup> has recently offered additional evidence in support of the concept of rheumatic fever as a reaction to hypersensitivity. Lesions resembling periarteritis nodosa were produced in experimental animals in whom serum sickness reactions had been induced by the injection of sterile horse serum or

<sup>14</sup> WEDUM, A. G., and WEDUM, B. G.: Serum precipitation reaction in rheumatic fever and in other conditions, *Proc. Soc. Exper. Biol. and Med.*, 1946, lxi, 432.

<sup>15</sup> CAVELTI, P. A., and CAVELTI, E. S.: Studies on the pathogenesis of glomerulo-nephritis. I. Production of auto-antibodies to kidney in experimental animals, *Arch. Path.*, 1945, xxxix, 148.

<sup>16</sup> CAVELTI, P. A., and CAVELTI, E. S.: Studies on the pathogenesis of glomerulo-nephritis. II. Production of glomerulonephritis in rats by means of auto-antibodies to kidneys, *Arch. Path.*, 1945, xl, 158.

<sup>17</sup> CAVELTI, P. A., and CAVELTI, E. S.: Studies on the pathogenesis of glomerulonephritis. III. Clinical and pathological aspects of the experimental glomerulonephritis produced in rats by means of auto-antibodies to kidney, *Arch. Path.*, 1945, xl, 103.

<sup>18</sup> CAVELTI, P. A.: Studies on the pathogenesis of rheumatic fever. I. Production of auto-antibodies to heart, skeletal muscle, and connective tissue in experimental animals, *Arch. Path.*, 1947, xlv, 1. II. Cardiac lesions produced in rats by means of auto-antibodies to heart and connective tissue, *Arch. Path.*, 1947, xlv, 13.

<sup>19</sup> CAVELTI, P. A.: Auto-antibodies in rheumatic fever, *Proc. Soc. Exper. Biol. and Med.*, 1945, lx, 379.

<sup>20</sup> KERR, W. J.: Pathogenesis of rheumatic fever, *Ann. Int. Med.*, 1948, xxix, 587.

<sup>21</sup> RICH, A. R.: Hypersensitivity in disease with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis, *Harvey Lect.*, 1946-47, xlii, 106.

## REVIEWS

*Fundamentals of Internal Medicine.* By WALLACE M. YATER, A.B., M.D., F.A.C.P. 1451 pages; 17 × 25.5 cm. 3rd Ed. Appleton-Century-Crofts, Inc., New York. 1949. Price, \$12.00.

This is an excellent and unusual textbook. It is intended primarily for the student and general practitioner—"to make readily available in simple form the essentials of the vast subject of internal medicine." This purpose is admirably achieved. The book is both compendious and comprehensive, and the authors, for the most part, have succeeded in combining a terse and business-like style with easy readability.

Innovations since the last edition include nearly 250 more pages; an increase in the number of contributing authors from 14 to 19; a detailed index at the beginning of each section; and the exclusive use of metric weights and measures. Two new and excellent chapters have been added, one on Chemotherapy and Therapy with Antibiotics, and one on Inhalational Therapy. The section on Electrocardiography has been expanded from a very inadequate dozen pages in the last edition to a scholarly thesis of some 50 odd pages. Unipolar leads are described and discussed in detail. Excellent as this section is, it far exceeds the bounds of the senior author's expressed purpose "to present the minimum amount of knowledge a medical student or general practitioner should have at his fingertips."

It is surprising to find that the concept of hypersplenism is practically ignored, and that the syndrome of acute focal nephritis is inadequately described. Again, the section on Medical Problems Incident to Flying is wordy and disproportionate, and all readers will not find the simultaneous treatment of acute and subacute bacterial endocarditis a happy experience.

While thoroughly up to date in therapy, the author does not "go overboard" after new remedies. Treatment sometimes tends to be sketchy, however, and it is noticeable that, for example, there is no mention of paludrine in malaria, hyoscine in seasickness or helium and oxygen in asthma.

In an authoritative textbook of this kind it is unfortunate to find terminological inaccuracies. As Somerset Maugham reminds us "words are tyrannical things, they exist for their meanings." It is therefore a pity that the misnamed syndrome, Erythromelalgia of the Head, is again invested with the sanctity of print. Such a title can only mean "painful red limbs of the head," which is anomalous to say the least. Again, under the heading Melena, no stretch of color vision can tolerate the inclusion of bright red bleeding. The misspelling of Achrestic, in both title and index, is minor but equally inaccurate.

A feature of this book is the valuable chapters on practical problems that the practitioners must daily face, but which are accorded too little attention in most textbooks and medical schools. Such are the sections on the Home Care of Patients with Contagious Diseases, Dietetics, and symptomatic and Supportive Treatment. In his final chapter, on The Physician Himself, Dr. Yater gives practical information and sound advice on many ethical and other questions which confront every doctor.

Other good features are the abundant illustrations, and the inclusion of tables of practical value (such as one comparing the cardiac glycosides, one on recommended therapy in infections, and several on the differential diagnosis of various disorders). A list of recommended texts is appended at the end of each section, and a section is devoted to Clinical Values and Useful Tables. In fact this book combines the good points of many others, for it is unusual to find so many excellent features and so much information in one volume of this size.

The sections on treatment and differential diagnosis are timely and complete. The authors discuss the problem of whether or not physical exertion can induce myocardial infarction or coronary occlusion, and conclude that this sequence of events is by no means uncommon.

S. S.

*Syphilis: Its Course and Management.* By EVAN W. THOMAS, M.D., Professor of Clinical Medicine, New York University College of Medicine; Director, Rapid Treatment Center and Visiting Physician, Bellevue Hospital, New York; Consultant, United States Public Health Service. 317 pages; 16 × 24 cm. Macmillan Company, New York. 1949. Price, \$5.50.

Dr. Thomas has presented a text which provides an understanding of the various stages of syphilis as far as our present day knowledge permits. There are 16 chapters which include the etiology of syphilis, its course, interpretation of the serologic tests, principles of treatment, methods of diagnosis of the various stages of syphilis and finally an excellent chapter on the public health aspects of the disease. The author's style is easy to follow and the wording is simple. The subject matter is adequately covered.

The author does not depend upon the statistics of others, but answers questions in the light of his own experience. For this he is well qualified. From the standpoint of a knowledge of the diagnosis of syphilis, the course of the disease and its treatment, this book is a valuable addition to the literature.

H. M. R., Jr.

*Industrial Fluorosis: A Study of the Hazard to Man and Animals Near Fort William, Scotland.* A Report to the Fluorosis Committee, Medical Research Council Memorandum No. 22. 131 pages; 15.5 × 24.5 cm. His Majesty's Stationery Office, London. 1949. Available from British Library of Information, 50 Rockefeller Plaza, New York. Price, 4 s. 0 d. net.

This report was issued by the Medical Research Council on the recommendations of their Fluorosis Committee to determine any effects of exposure to fluorine compounds on workers employed in factories manufacturing aluminum by an electrolytic process, and also to determine any effects upon those living in the neighborhood of such factories.

The paper-bound volume is divided into five sections and a summary as follows: Studies of contamination from the standpoint of topography, geology, meteorology, etc.; the effects of fluorine compounds upon animals in the area; clinical, radiological, hematological and biochemical findings in selected groups of individuals living in the area; the dental condition of adults and school children in the Fort William area; physical properties of bone in fluorosis. Each section was contributed by special workers. The volume contains 13 plates and 3 maps. The appendix includes an extensive review of the literature dealing with the toxicity of fluorine compounds and details of analytical methods.

From the mass of data collected, certain general conclusions are of interest. Workers from furnace rooms, where concentrations of fluorine as high as 3.6 mg. per cubic meter were encountered, inhale considerable quantities of fluorine. The excretion of fluorine in their urine roughly parallels the intensity of exposure. Workers exposed for a number of years to these conditions show bone changes of the type now generally recognized to be produced by fluorosis. Despite these changes none of the workers examined was found to suffer clinical disability. The recommendations of the Committee, however, are that determined efforts be made to reduce the fluorine exposure. The hazards to the surrounding population appear to be slight but con-

- Cardiovascular Disease: Fundamentals, Differential Diagnosis, Prognosis and Treatment.* By LOUIS H. SIGLER, M.D., F.A.C.P., Attending Cardiologist and Chief of Cardiac Clinic, Coney Island Hospital, etc. 551 pages; 23.5 × 15.5 cm. 1949. Grune & Stratton, Inc., New York. Price, \$10.00.
- Clinical Allergy. 2nd Edition.* By LOUIS TUFT, M.D., Assistant Professor of Medicine, Temple University School of Medicine, etc. 690 pages; 24 × 16 cm. 1949. Lea & Febiger, Philadelphia. Price, \$12.00.
- Conference on Metabolic Aspects of Convalescence. Transactions of the Sixteenth Meeting, New York, N. Y., October 27-28, 1947.* Edited by EDWARD C. REIFENSTEIN, JR., M.D., Sloan-Kettering Institute, New York. 168 pages; 23 × 15.5 cm. (paper-bound). 1949. Josiah Macy, Jr. Foundation, New York. Price, \$3.00.
- Conference on Metabolic Aspects of Convalescence. Transactions of the Seventeenth Meeting, New York, N. Y., March 29-30, 1948.* Edited by EDWARD C. REIFENSTEIN, JR., M.D., Sloan-Kettering Institute, New York. 246 pages; 23 × 15.5 cm. (paper-bound). 1949. Josiah Macy, Jr. Foundation, New York. Price, \$4.00.
- Diagnostic Tests for Infants and Children: Principles, Clinical and Laboratory Procedures, Interpretation.* By H. BEHRENDT, M.D. 529 pages; 23.5 × 16 cm. 1949. Interscience Publishers, Inc., New York. Price, \$7.50.
- The Epitome of Andreas Vesalius.* Translated from the Latin with Preface and Introduction by L. R. LIND, Ph.D., University of Kansas; with Anatomical Notes by C. W. ASLING, M.D., Ph.D., University of California, and a Foreword by the Late LOGAN CLENDENING, M.D. 131 pages; 26 × 19.5 cm. 1949. The Macmillan Company, New York. Price, \$7.50.
- Geriatric Medicine. 2nd Edition.* Edited by EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P., Attending Internist, Suburban Hospital, Bethesda, Maryland (Chairman Staff, 1945-47), etc. 773 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$12.00.
- Hematology for Students and Practitioners.* Revised 2nd Edition. By WILLIS M. FOWLER, M.D., Professor of Internal Medicine, University of Iowa; with a Chapter by ELMER L. DEGOWIN, M.D., Associate Professor of Internal Medicine, University of Iowa. 535 pages; 24 × 16 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers. Price, \$8.50.
- Internal Medicine, being Section VI of Excerpta Medica.* Volume II, No. 10, October, 1948. Under the General Editorship of M. W. WOERDEMAN, M.D., F.R.N.A.S., Professor of Anatomy and Embryology in the University of Amsterdam. 159 pages; 25 × 16.5 cm. (paper-bound). October 1948. The Williams & Wilkins Company, Baltimore. Price, By subscription, \$37.50.
- Manual of Medical Emergencies.* By STUART C. CULLEN, M.D., Professor of Surgery; Chairman, Division of Anesthesiology, State University of Iowa College of Medicine, and E. G. GROSS, M.D., Professor and Head of Department of Pharmacology, State University of Iowa College of Medicine. 267 pages; 18.5 × 12.5 cm. 1949. The Year Book Publishers, Inc., Chicago. Price, \$3.75.
- Medical Etymology: The History and Derivation of Medical Terms for Students of Medicine, Dentistry, and Nursing.* By O. H. PERRY PEPPER, M.D., Professor of Medicine, University of Pennsylvania. 263 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$5.50.



# COLLEGE NEWS NOTES

## PROPOSAL OF CANDIDATES

The By-Laws of the American College of Physicians require that proposals of candidates for election to Associateship or Fellowship be filed at least 60 days in advance of action by the Credentials Committee. The next meeting of the Committee is scheduled for November 12, and to receive action at that meeting proposals must therefore be filed with the College Headquarters not later than September 12, 1949.

---

## RESEARCH FELLOWSHIPS APPLICATIONS

Applications are being received to October 1, 1949, for the Research Fellowships in Medicine which the American College of Physicians will make available for the year beginning July, 1950. These Fellowships provide an opportunity for young physicians who are training for academic careers in Internal Medicine or Pediatrics to gain a year of experience in laboratory or clinical investigation. All applications received by October 1 will be reviewed by the Committee on Fellowships and Awards at a meeting to be held on November 12; the Committee will make its recommendations to the Board of Regents the following day, and applicants will be notified shortly thereafter.

The stipends awarded will be in the range of \$2,200 to \$3,200, depending upon the individual needs of the applicants. Application forms may be obtained from the American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

---

## DR. DRENCKHAHN APPOINTED GOVERNOR FOR SOUTHERN ILLINOIS

In accordance with provisions of the By-Laws, President Fitz has appointed Charles H. Drenckhahn, M.D., F.A.C.P., 602 W. Urbana Ave., Urbana, Ill., to serve as A.C.P. interim Governor for Southern Illinois until the next Annual Business Meeting of the College on April 20, 1950, during the Annual Session in Boston. Dr. Drenckhahn succeeds in this post Dr. Cecil M. Jack, F.A.C.P., Decatur, Ill., who gave devoted service to the College as Governor from 1941 until his untimely death on June 28, 1949.

Dr. Drenckhahn is a graduate of the University of Minnesota Medical School and a Diplomate of the American Board of Internal Medicine. He is a member of the staff of the Carle Memorial Hospital and has been a Fellow of the College since 1939.

---

## 1949 A.C.P. MEMBERSHIP DIRECTORY

Work on the first complete Directory of the American College of Physicians to be published since 1941 has progressed satisfactorily and is expected to be concluded by the end of September. Copies will be mailed at the earliest possible date to all members and others who have sent their prepublication orders to the College Headquarters. The Directory will be issued in a limited edition only; members who will want but have not yet placed their orders should do so without delay to avoid the possibility of disappointment. The prepublication price, to be billed at time of shipment, is \$4.00 a copy to members; \$5.00, to non-members and institutions.

---

## AUTUMN AND WINTER REGIONAL MEETINGS OF THE COLLEGE

*Montana and Wyoming, Great Falls, Mont., September 9, 1949.* Dr. Harold W. Gregg, F.A.C.P., Butte, Mont., Governor for the two States, is planning a program

*Puerto Rico, San Juan, October 16, 1949.* R. Rodriguez-Molina, M.D., F.A.C.P., Governor, will initiate Regional Meetings in Puerto Rico on this date. The program will be published in a later issue.

*Midwest, Indianapolis, November 19, 1949.* J. O. Ritchey, M.D., F.A.C.P., Indianapolis, Governor for Indiana, will be Chairman of this meeting, to which College members from Illinois, Indiana, Michigan, Minnesota and Wisconsin will come. The Governors from all these States will cooperate in setting up the program for the 1949 version of one of the largest of the College's Regional Meetings.

*New Jersey, Newark, November 30, 1949.* Under the Governorship of Dr. George H. Lathrope, F.A.C.P., Newark, and with Dr. J. F. Pessel, F.A.C.P., Trenton, as Chairman of the Program Committee, arrangements are progressing satisfactorily for another of the fine New Jersey Regional Meetings. It is expected that President Reginald Fitz, F.A.C.P., Boston, Secretary-General George Morris Piersol, M.A.C.P., Philadelphia, Regent Edward L. Bortz, F.A.C.P., Philadelphia, and Treasurer William D. Stroud, F.A.C.P., Philadelphia, will be among the guest speakers.

*Southeastern States, Birmingham, Ala., December 10, 1949.* This meeting will be held at The Medical College of Alabama and the Thomas Jefferson Hotel, with arrangements by Dr. E. Dice Lineberry, F.A.C.P., Birmingham, local Governor, Dr. Edgar G. Givhan, Jr., F.A.C.P., Birmingham, General Chairman, and Dr. Duward O. Wright, F.A.C.P., Birmingham, Chairman of the Arrangements Committee. This Regional Meeting will be a part of and will conclude the A.C.P. Postgraduate Course on Blood Dyscrasias, to be given at The Medical College of Alabama by James B. McLester, M.D., F.A.C.P., Director, December 6-10, 1949.

*Kansas, Topeka, March 17, 1950.* Dr. William C. Menninger, F.A.C.P., Topeka, Governor for Kansas, will prepare the program. Dr. Hugh J. Morgan, F.A.C.P., Nashville, Tenn., Regent and Past-President of the College, has agreed to attend as guest speaker.

*Other Meetings.* The Arizona and Virginia sections of the American College of Physicians plan to hold their Regional Meetings in the late winter or early spring of 1950, but have not as yet selected definite dates.

---

#### ADDITIONAL LIFE MEMBERS

Grateful acknowledgment is made to the following Fellows of the College for their recent subscriptions to Life Membership:

W. E. Bayley, La Fayette, Ind.  
 Joseph Augustine Lundy, Worcester, Mass.  
 Terence Lloyd Tyson, New York, N. Y.  
 Joseph Edward Walther, Indianapolis, Ind.

---

#### A.M.A. DISTINGUISHED SERVICE MEDAL

The American College of Physicians takes pride in the recent award of the Distinguished Service Medal of the American Medical Association to one of its outstanding Fellows, Seale Harris, M.D., Birmingham, Ala.

---

Myron M. Weaver, Assistant Dean of Medical Sciences and Associate Professor of Medicine and Public Health, University of Minnesota, has accepted the Deanship of the new Faculty of Medicine of the University of British Columbia and assumed that position at Vancouver on July 1. It is hoped that plans for the development of the new medical school will be presented from time to time in this publication for the many readers who will be interested in them.

## ELECTION OF OFFICERS, AMERICAN MEDICAL ASSOCIATION

At the recent annual session of the American Medical Association, held in Atlantic City, N. J., in June, Dr. Ernest E. Irons, F.A.C.P., Chicago, was installed as President for 1949-1950. Dr. Elmer L. Henderson of Louisville, Ky., was elected President-Elect to succeed Dr. Irons. Dr. James Francis Norton, Jersey City, N. J., was elected Vice President. Dr. George F. Lull, F.A.C.P., and Dr. Josiah J. Moore, F.A.C.P., both of Chicago, were re-elected as Secretary and Treasurer, respectively. Francis F. Borzell, M.D., F.A.C.P., Philadelphia, was elected to succeed himself as Speaker of the House of Delegates, and James R. Reuling, M.D., F.A.C.P., Bayside, N. Y., was elected as Vice Speaker. Louis H. Bauer, M.D., F.A.C.P., Hempstead, N. Y., was re-elected as a Trustee and Thomas P. Murdock, M.D., F.A.C.P., Meriden, Conn., was elected a member of the Judicial Council.

Chicago was selected as the site of the 1952 annual session.

The following Fellows of the College were elected on June 28 by the Section on Internal Medicine: Arthur Bloomfield, San Francisco, Chairman; Ralph A. Kinsella, St. Louis, Vice Chairman; Walter L. Palmer, Chicago, Secretary; Charles T. Stone, Galveston, Representative to the House of Delegates; William D. Stroud, Philadelphia, Alternate; Cecil J. Watson, Minneapolis, M. A. Blankenhorn, Cincinnati, and Arthur Bloomfield, San Francisco, to the Executive Committee.

## SEPARATE MEDICAL SERVICE FOR THE U. S. AIR FORCE

As of July 1, 1949, a separate medical service has been authorized for the U. S. Air Force. Major General Malcolm C. Grow has been designated as the Surgeon General and given an organizational and functional position directly under the Chief of Staff of the Air Force. It has been planned that physicians in the Air Force will have opportunity to gain advanced training in clinical medicine and in the investigation of problems important to aviation medicine. It is anticipated that the majority of the Army medical officers now serving with the Air Force will be transferred to the Air Force by the end of July, but it is possible that for some longer period some Army personnel will continue to be on duty with the Air Force without being commissioned therein.

## NATIONAL HEART INSTITUTE GRANTS

National Heart Institute grants of more than \$1,200,000 to support heart disease research work in medical schools and hospitals in twenty-one states, the District of Columbia and Canada have been announced by the Federal Security Administrator recently. The grants were approved by Surgeon General Leonard A. Scheele, F.A.C.P., of the Public Health Service, following recommendation by the National Advisory Heart Council.

Dr. C. J. Van Slyke, Director of the National Heart Institute, states that only a portion of the federal funds to be awarded for heart disease research during the current fiscal year is represented in the above. Additional grants for new heart research and for construction of heart research facilities and laboratories are expected to be announced shortly.

Established last August (1948) under authority of the National Heart Act, the National Heart Institute is one of the National Institutes of Health, the research arm of the Public Health Service, with headquarters in Bethesda, Md. In addition to conducting scientific research in its own laboratories, the Institute administers federal funds supporting research and training related to the cause, prevention, and methods of diagnosis and treatment of heart disease in outside institutions throughout the country.

## OBITUARIES

## DR. GEORGE L. COOK

The death of Dr. George Lindsay Cook on March 8, 1949, brought a deep sense of loss to a host of friends and patients throughout Florida. Dr. Cook had practiced in Tampa since 1925, and held great influence in medical affairs in his community. His courtesy, unfailing kindness and sympathy endeared him to a host of friends.

He was born in Augusta County, Va., on October 10, 1886. He took his academic training at the University of Virginia, and graduated in medicine from the Medical College of Virginia in 1913. He interned at the Gouverneur and Woman's Hospitals in New York between 1914 and 1916. From 1917 to 1919, he served as a Captain in the Medical Reserve Corps of the U. S. Army. After completing his military service, he spent two years at the Bellevue and Willard Parker Hospitals in New York City. He entered the practice of pediatrics in Atlanta, Ga., in 1921, and moved to Tampa in 1925.

Dr. Cook was attending pediatrician to the Tampa Municipal and St. Joseph's Hospitals, and was a member of the American Academy of Pediatrics. He became a Fellow of the American College of Physicians in 1929 and a Diplomate of the American Board of Pediatrics in 1934.

Dr. Cook died of a coronary occlusion after having suffered a previous attack three years before. Although realizing the danger, he steadfastly refused to curtail his work during the period of medical emergency. His loss will be deeply felt.

WILLIAM C. BLAKE, M.D., F.A.C.P.,  
Governor for Florida

## DR. SAMUEL ELGART

Dr Samuel Elgart, born in Providence, R. I., September 20, 1911, died in Cincinnati, Ohio, on June 18, 1949.

Dr. Elgart received his B.S. degree from Tufts College in 1934 and his M.D. degree from Tufts College Medical School in 1938. His internship was served at Beth Israel Hospital, Boston, 1938-39, and he continued his postgraduate training in medicine and biochemistry at Duke University the following year. For two years, 1940-42, he was associated with the May Institute of Medical Research and the University of Cincinnati College of Medicine, in biochemistry. Since 1943 he had been on the Staff of the Cincinnati General and Jewish Hospitals and had attended the Beckman Dispensary, the Hamilton County Home and Chronic Disease Hospital. Since 1944 he had been an Instructor in Medicine at the University of Cincinnati College of Medicine.

Dr. Elgart was always interested in clinical investigation and spent the major part of his active medical years in the study of endocrinologic problems, more recently utilizing radioactive isotope technics. He received great personal satisfaction in his teaching opportunities, whether they represented the teaching of under-graduate medical students, participation in postgraduate medical courses, or the teaching of student nurses. His teaching and investigative career has been unfortunately prematurely ended, and his many friends and professional associates feel that medicine has sustained a very real loss in his passing.

Dr. Elgart was elected an Associate of the American College of Physicians in April, 1938. He was a Diplomate of the American Board of Internal Medicine and was active in the American Diabetes Association together with other local and national medical societies.

CHARLES A. DOAN, M.D., F.A.C.P.,  
Governor for Ohio

## ABRIDGED MINUTES OF THE BOARD OF REGENTS

NEW YORK, N. Y.

APRIL 1, 1949

The third meeting of the Board of Regents during the 30th Annual Session, and the first meeting of the new Board of Regents, was held at the Waldorf-Astoria Hotel, New York, N. Y., Friday, April 1, 1949, convening at 1:40 p.m., with President Reginald Fitz presiding and with Mr. E. R. Loveland acting as Secretary. The following were present:

Reginald Fitz, *President*; George F. Strong, *First Vice President*; Roy R. Snowden, *Second Vice President*; Turner Z. Cason, *Third Vice President*; David P. Barr, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Walter B. Martin, LeRoy H. Sloan, Harold H. Jones, T. Grier Miller, Charles F. Moffatt, and Charles A. Doan, *Vice Chairman, Board of Governors*.

The Secretary read an abstract of the Minutes of the preceding meeting of the Board of Regents, which were accepted as read.

President Fitz introduced Dr. Fay A. LeFevre, Vice President and Chairman of the Executive Committee of the Academy of Medicine of Cleveland, Dr. Vernon C. Rowland, F.A.C.P., of Cleveland, and Mr. Edward Brennan, of the Cleveland Convention and Visitors' Bureau. Each of them extended an invitation to the College to hold its 1951 Annual Session in Cleveland, and they presented such information as desired about the facilities available. They were all cordially thanked for their invitation, and were told that the Board would take the Cleveland invitation up with other invitations to be considered later in the meeting.

In accordance with the chief purposes of this meeting of the Board of Regents, the President proceeded with the organization of the Board and its Committees for the succeeding year.

Dr. Walter B. Martin nominated Dr. George Morris Piersol for re-election as the Secretary-General; he was seconded by Dr. A. B. Brower, and was unanimously re-elected.

Dr. T. Grier Miller moved the re-election of Dr. William D. Stroud as Treasurer. The nomination was seconded, and Dr. Stroud was unanimously so re-elected.

Dr. Chester S. Keefer was nominated and seconded as the General Chairman of the Boston Annual Session, 1950, and his election was unanimously confirmed.

In accordance with regulations of the By-Laws and/or the Minutes of the Board of Regents, committees for 1949-1950 were elected or appointed. (Inasmuch as the personnel of these committees have previously been published in this journal, this portion of the proceedings is omitted.)

Dr. Charles A. Doan, as Vice Chairman of the Board of Governors, in the absence of the Chairman, Dr. Walter L. Palmer, reported for that Board. He requested some consideration of some kind of limitation of the attendance at the Annual Sessions of the College, so that members would have access to and seats in the main auditorium and other scheduled programs. Accordingly, the Board of Governors had adopted a resolution suggesting to the Board of Regents as an experiment at the next Annual Session that attendance be limited to Masters, Fellows and Associates and guests specifically invited and sponsored by these members. The Board of Governors felt the sessions were becoming so large that meeting facilities are inadequate, and some effort must be made to hold the attendance down to the available facilities. The suggestion was that guests that are sponsored by members shall notify the Executive Office in advance. It had been disclosed at the New York Session that more than half of the guests came unsponsored.

help Army training programs, but results had thus far not proved very satisfactory. He said a group of younger men in New York were now preparing a proposal, copy of which he distributed, but it had nothing to do officially with the College. These gentlemen wished to bring this up through us to the attention of teaching staffs in medical schools, with the hope that more progress can be made toward making the Army more worth while educationally. He said that they hoped that if the deans and heads of departments realize that the younger men themselves were really concerned about this, there might be some impetus to the promotion of the program.

Dr. Walter B. Martin stated that there is a great shortage of trained men in the Army hospitals in the occupied zones, and that in some of the small hospitals there is no one between a commanding officer and an interne—often no trained surgeon, not even a trained interne, not a single ophthalmologist and possibly one trained orthopedist on duty. Anything that could be done to remedy that condition would certainly be well worth while, he thought.

Dr. George F. Strong referred to the acute conditions in Australia, where their isolation is possibly greater than ever before. He said they are almost entirely cut off from America and Canada. The dollar situation is such that they cannot even subscribe to medical journals from this Continent. He raised the question as to whether the American College of Physicians, could not sponsor visiting professorships by which two or three men might visit Australia annually, or semi-annually, as a gesture of friendship and coöperation. Dr. Strong suggested the matter be given consideration and possibly referred to some appropriate committee for study.

Dr. Cyrus C. Sturgis suggested the possibility of interesting the Kellogg Foundation in one or two fellowships for Australian and New Zealand men. He said the Foundation is interested in extending its fellowships to Canada, but could not express an opinion as to their interest in extending them to Australia.

Dr. Strong clarified his proposal by saying that he was not thinking especially of bringing their men here, but of sending a group of competent men on a post-graduate tour of Australia.

On motion by Dr. George F. Strong, seconded by Dr. Walter B. Martin, and carried, it was

RESOLVED, that the Committee on Fellowships and Awards make a survey of the possibilities, both with respect to bringing people to America from Australia and of sending teachers to Australia, and to report back at the next meeting of this Board.

There being no further business, the meeting *adjourned* at 2:20 o'clock.

Attest: E. R. LOVELAND,

Secretary

. . . President Fitz, following the meeting and in accordance with earlier directions of the Board of Regents concerning representation on the Advisory Council on Medical Education, appointed Dr. Marion A. Blankenhorn, Cincinnati, Ohio, as the College representative. . . .

## ABRIDGED MINUTES OF THE BOARD OF GOVERNORS

NEW YORK, N. Y.

MARCH 30, 1949

A regular meeting of the Board of Governors, during the 30th Annual Session, convened at one o'clock, March 30, 1949, at the Waldorf-Astoria Hotel, New York, N. Y., with Dr. Walter L. Palmer, Chairman of the Board, presiding and with Mr. E. R. Loveland acting as Secretary. The following were in attendance:

Asa L. Lincoln, New York .....	NEW YORK (Eastern)
Charles A. Doan, Columbus .....	OHIO
Howard P. Lewis, Portland .....	OREGON
David W. Carter, Jr., Dallas .....	TEXAS
Karver L. Puestow, Madison .....	WISCONSIN
John W. Scott, Edmonton .....	ALBERTA and BRITISH COLUMBIA
Charles H. A. Walton, Winnipeg .....	MANITOBA and SASKATCHEWAN
*James O. Gillespie .....	UNITED STATES ARMY
Paul B. Magnuson .....	UNITED STATES VETERANS ADMINISTRATION

*Guest:*

Walter W. Palmer .....President

By resolution regularly carried, the Minutes of the preceding meeting were merely abstracted by the Secretary.

Chairman Walter L. Palmer introduced President Walter W. Palmer, who responded with a few remarks.

The Chairman then proceeded with the election of a Vice Chairman to succeed Dr. Edward L. Bortz, whose term as Governor had expired.

. . . Two candidates were nominated as Vice Chairman; written ballots were cast; and Dr. Charles A. Doan, Governor for Ohio, was declared elected. . . .

Chairman Palmer then proceeded to the election of a representative from the Board of Governors to fill the vacancy on the Committee on Credentials, to succeed Dr. Wallace M. Yater, whose term expired.

Dr. William C. Chaney nominated Dr. J. Murray Kinsman from Kentucky. Dr. Wallace M. Yater moved that the nominations be closed. The motion was seconded by Dr. Edgar Hull, voted upon and carried, and the Secretary was instructed to cast one ballot for the election of Dr. Kinsman.

Chairman Palmer then called for the appointment of a member on the Advisory Committee on Postgraduate Courses to succeed Dr. Edward L. Bortz, who was retiring from the Board of Governors.

(Chairman Palmer obtained permission to delay his appointment until after the elections at the Annual Business Meeting on Thursday, March 31. Subsequently he appointed Dr. Thomas M. McMillan, of Philadelphia, newly elected Governor for Eastern Pennsylvania, to succeed Dr. Bortz not only as a member of the Committee, but as Chairman.)

Chairman Palmer then opened the meeting for general discussions of problems of the College, and asked the Secretary, Mr. E. R. Loveland, to introduce the subject of Regional Meetings.

Mr. Loveland pointed out that often the dates of Regional Meetings either conflict or are so close together that it makes it difficult to arrange for the President, President-Elect, or Officers, to accept speaking engagement for the Regional Dinner-Meeting, and Regents in those instances must be called upon. He asked the Governors to keep him advised longer in advance, if possible, concerning the dates of their meetings and their requirements. He restated that the Central Office is prepared to print and distribute all Regional Meeting programs, to furnish a speaker for the dinner-meeting and to help in such other respects as Governors desire.

Chairman Palmer then asked for a discussion of the whole subject of the rôle of the Governor in endorsing candidates for membership in the College, and asked Dr. Wallace M. Yater, the retiring member of the Credentials Committee, to introduce the discussion.

Dr. Yater said that from his experience and observation, he felt it takes too long for a new Governor to know what his duties are and all the details connected

\* Alternate.

the time has come to put an age limit on candidates. When one figures that a young man is out of his residency probably at the age of thirty-one and is eligible for his Board examination at thirty-three, he moves on to a Fellowship in the College at thirty-six to thirty-eight. I think, however, that that is a good age period for these young men.

DR. PAUL F. WHITAKER (Governor for NORTH CAROLINA): Mr. Chairman, I would like to speak in support of Dr. Lathrope's suggestion. In North Carolina we have three teaching institutions. Often a young man who is doing research work or pursuing further training writes to me to determine the policy of the College in regard to admission. It is our custom to inform him that the candidate should complete his training and be established in a permanent location. I agree with Dr. Lathrope that many men feel that because they have been certified by the American Board of Internal Medicine they have automatically become eligible for Fellowship in the College. I know of no other organization that commands more respect in our part of the country than does the College, and I feel that putting an age limit of thirty or thirty-one for Associateship would be a wise policy and would strengthen the College.

Chairman Palmer then asked Dr. Lathrope to discuss the matter of permanent location as a prerequisite for Associateship.

DR. LATHROPE: We feel that is important. The candidate should be located in practice or some type of work sufficiently long to be known by our Fellows in his community, so that there are local men to sponsor him and local men to support his candidacy. The Credentials Committee wants to know what kind of medicine he is practicing, whether he is ethical, what sort of a citizen he is. We think he should be established for two years in one place.

While I am speaking, may I say a word in response to Dr. Murdock about older candidates? The older men, around fifty to sixty years of age, who have been handed back by the Committee are usually men who have not as yet passed their Board examinations, and the Committee feels that after forty-five it is pretty difficult for them to do so, although some men do. Therefore, the Committee does not wish to admit to Associateship any candidate until he has a reasonable opportunity and expectancy to qualify for Fellowship three to five years hence.

DR. LELAND P. HAWKINS (Governor for Southern CALIFORNIA): Would it be possible, in the next communication that goes to the membership, for the Credentials Committee to put in an announcement with that information included to each member, reiterating what the qualifications are for Associateship and for Fellowship, so that we, as Governors, will not get proposals of candidates who really are not ready for membership? Once these proposals reach us—and they oftentimes come on the basis of friendship—the Governors may be embarrassed to refuse endorsement. I think the Fellows-at-large need some education concerning the requirements.

DR. LATHROPE: Mr. Chairman, as you all know from the discussion at our previous meeting, the Executive Secretary and the Chairman of the Committee on Credentials are going to prepare a specific, suggestive outline of the requirements that an Associate must fulfill to become a Fellow. I believe that this communication should include something about the requirements for Associateship too—that the candidate should have already attained eligibility for admission to his Board examinations and that he should have been established at least a year and one-half, or two years, in one place for practice, so that the men in his surrounding area shall know what sort of work he does and what sort of a man he is. Endorsing candidates is a responsibility of the Governors entirely. They are not under obligation to endorse any candidate who is not qualified, and they should be perfectly free to return proposals to the sponsors, with an explanation of why the candidate is not eligible.

DR. WALLACE M. YATER: Mr. Chairman, there is another reason for requiring two years of residency in the community. At the end of that two years, the young



in without instruction, other than that furnished by the Secretary. I am opposed to the age limit for membership in the College.

DR. EDGAR HULL (Governor for LOUISIANA): We should guard against Associateship or Fellowship becoming more or less automatic. The more rules we have pertaining to Board Certification, pertaining to age, pertaining to the number of papers that the candidate must write, pertaining to the number of years which he must have practiced in a community, the more apt we are to have membership in the College become automatic, in which case we would have no need for a Board of Governors and little or no need for a Committee on Credentials. Personally, I favor leaving the rules as they are and having the Governors of the College realize that they have a responsibility in determining whom they should and should not endorse for membership, and the Committee on Credentials has a similar, but even greater, responsibility. I for one am not irked at all when the Credentials Committee turns down a candidate whom I endorsed. I personally favor leaving the rules as they are, and still having the Board of Governors and the Committee on Credentials do a job.

DR. ARLESS A. BLAIR (Governor for ARKANSAS): If you put the age limit too far away from the candidate's training, he is going to find it more difficult to pass his Board examinations. That is the principal objection I have to an age limit.

DR. RADL: Under the present plan of operation, the average candidate for Fellowship qualifies possibly at the age of thirty-six. We should be careful not to deprive the younger man of the benefits of the College—the Regional Meetings, Annual Meetings, Postgraduate Courses, etc.

DR. RALPH A. KINSELLA (Governor for MISSOURI): Educational opportunity, I think, is probably more important in establishing a ceiling for admitting Associates rather than a minimal age.

The motion before the Board was now voted upon and defeated.

Chairman Palmer then asked for discussion of other problems or policies.

DR. GEORGE H. ANDERSON (Governor for WASHINGTON): Something should be done about making more seats available for members at the General Sessions. Many of us have had to stand up. Someone has thought that by raising the fee for non-members it would remedy this situation, but I contend it would accomplish nothing. I believe the guests will come anyhow.

DR. YATER: Mr. Chairman, the Credentials Committee recommended recently that attendance be limited to members and actually invited guests of members, but that suggestion was defeated at the joint meeting of the Governors and Regents on March 27. Therefore, the matter will have to be reopened if anything further is to be done about it. It seems unfortunate to me that there are so few cities in which the College can now meet for its Annual Sessions. If we could limit the non-member attendance we could get around the country better. It would be a more healthy condition for the College. In which cities can the College now be accommodated?

MR. LOVELAND: Philadelphia, Cleveland, Boston, St. Louis, Minneapolis, St. Paul, San Francisco are the only cities that have adequate auditoriums. We have never considered Atlantic City as a possibility, because it lacks hospital clinical facilities. Our great problem is the large number of guests. At this New York meeting approximately half of the doctor registration is made up of non-members.

DR. MURDOCK: I move that the Board of Governors go on record to the Board of Regents that in the future the meetings be limited only to Fellows and Associates and guests actually invited by the Fellows, Masters and Associates.

The motion was seconded by Dr. Edward C. Reifenshtein, Sr., Governor for Western New York, and after discussion it was voted upon and carried.

DR. ROBERT WILSON, JR. (Governor for SOUTH CAROLINA): Mr. Chairman, it seems to me that there are several sides to the whole question—one of which is to retain the type of meeting we are having at the moment, of which every one is in

"During the year 1948 the College added to its General Fund \$29,045.79, to its Endowment Fund \$24,055.73, and received a gift in trust of \$2,500.00, a second installment on an educational trust fund of \$10,000.00 subscribed by Dr. A. B. Brower, one of our Fellows.

"The gross assets of the College, as of December 31, 1948, amounted to \$664,158.63, divided as follows:

General Fund .....	\$361,790.75
Endowment Fund .....	286,940.80
James D. Bruce Fund .....	10,395.83
A. Blaine Brower Fund .....	5,031.25

"The College operated entirely within its budget for the year. Its investments are supervised by an Investment Counselor and the Committee on Finance, and are carefully reviewed periodically. As of December 31, 1948, the College held investments at book value totalling:

Endowment Fund .....	\$294,277.79
General Fund .....	187,504.22
	<hr/>
	\$481,782.01
	<hr/>

"The current average yield as of March 10, 1949, is 4.05 per cent.

"The Board of Regents has approved a budget for 1949 calling for an estimated income of approximately \$217,000.00 and an estimated expenditure of approximately \$206,000.00, leaving an anticipated balance of approximately \$11,000.00. The financial policies of the College are at all times conservative."

By resolution regularly moved, seconded and carried, the Treasurer's report was accepted.

Mr. E. R. Loveland presented the following annual report of the Executive Secretary:

"Mr. President, Fellows and Masters, the report of the Executive Secretary is supplementary to those of the President, Secretary-General and Treasurer.

"There has been a gradual levelling off and a return to more normal conditions this past year from those of the War and immediate post-war years. We believe the operation of the College and its activities may now be considered approaching a normal state of affairs. We observe, however, that in spite of the War and its attendant abnormalities, the College has made great strides since 1942.

"Since our last Annual Session the fine addition to our Headquarters, offices and an Assembly Room, have been concluded and occupied. Our Assembly Room will be utilized for our Postgraduate Course in Cardiovascular Disease at Philadelphia, opening on May 2. This addition was a necessity and a wise investment.

"During 1948 we conducted 28 formal Regional Meetings, largely of the single State character, but in several instances of the multi-State character. These meetings grow in their popularity and practicability. We are sure they make a real contribution to the College work.

"The ANNALS OF INTERNAL MEDICINE continues to grow in stature and in popularity, although with the increase in the subscription rate from \$7.00 to \$10.00 per annum, occasioned by a sharply increasing cost over the last three or four years, the circulation has maintained its level of somewhat over 12,000 copies per month. This is gratifying, for one might have anticipated a reduction.

"During September, 1948, we republished the Membership Roster. We are pleased to announce that the Board of Regents has authorized the publication of a new and entirely revised full Directory of the College during the coming summer. The cost is estimated at from \$17,000.00 to \$20,000.00, but we have already received

*"Fellowships:* The College is maintaining at the present time 6 active Research Fellowships, and has voted 7 new Research Fellowships, starting July 1, 1949. The annual budget for these fellowships is approximately \$20,000.00. A plan has been consummated with the W. K. Kellogg Foundation for the College to expand its fellowship program to Latin American Countries, affording an opportunity for the further training of Latin American young men for a career in teaching and research in their home lands. They will be carefully selected, brought to the United States for study for a period of one or more years, under supervision of the American College of Physicians and the Kellogg Foundation, and the Kellogg Foundation has generously agreed to supply the necessary funds.

"As gratifying as may be the above-mentioned educational activities of the College, its Annual Sessions should not be overlooked as the most significant and far-reaching contribution of the College. The current Session is a further outstanding example of what has been accomplished by a year's well coördinated effort. We are mindful of our great debt to those who have made this New York Session possible."

DR. PIERSOL: Now, Mr. President, through this past year you have guided the destiny of this organization and have carried out its purposes with good judgment and exceptional ability. Those of us whose privilege it has been to be closely associated with you in the conduct of the College are keenly aware of the never failing courtesy, forbearance and coöperation that have marked your every act. Therefore, it is our desire to express to you in some enduring way our appreciation and affection, and so, on behalf of your fellow Officers, the Regents and Governors of the American College of Physicians, it is our pleasure at the present time to present you with this gavel. (Applause.)

PRESIDENT PALMER: Dr. Piersol, I do appreciate this recognition, and I shall treasure this token as long as I live. I do want to say this to the College. I do not know of any year in my life which has been so instructive, so illuminating and so valuable as I have had in my association with the College members, particularly in the Regional Meetings. I have gotten an entirely different idea of what the College means to its members.

Before relinquishing my Presidency and introducing your new President, I should like to say a few words about him. At the end of my second year in Harvard Medical School his father gave the first clinic that I ever attended. It was a clinic which I shall never forget. Dr. Fitz' father was a master of presentation and stimulation in this work. Later on I had the pleasure to serve with Dr. Fitz, your new President, as Associate at Massachusetts General Hospital. He was a year ahead of me, and I always valued his association greatly. After he graduated from the Massachusetts General Hospital he served as assistant resident at Hopkins, then went back to Brigham and then to the Rockefeller Hospital as assistant resident and finally as resident at Massachusetts General. During World War I he served in the Army as a Medical Officer. He spent the years 1920 through 1922 at the Mayo Clinic, later coming back to Boston as the Director of the Medical Service, associated with Boston University, and thereafter arriving at his position in the Harvard Medical School in 1929 as a Lecturer in the History of Medicine and Assistant to the Dean.

Dr. Fitz has served the College long and well. He conducted the clinical program in Rochester, Minn., at the Sixth Annual Session of the College. Nineteen years later he performed a similar function in Boston. For years he has been on the Board of Regents. He has been Chairman of several of their Committees, and is an efficient Chairman. It is with great pleasure that I introduce my old friend and colleague, Dr. Reginald Fitz, your new President.

(The members arose and applauded.)

The Chairman inquired for nominations from the floor; there being none, a motion was made, seconded and carried instructing the Secretary to cast a single ballot for the election of all the above Officers.

DR. PINCOFFS (Continuing): The Committee places in nomination five names for election as Regents of the American College of Physicians, for a term expiring in 1952:

Dr. William S. McCann, Rochester, N. Y.  
 Dr. T. Grier Miller, Philadelphia, Pa.  
 Dr. Charles F. Moffatt, Montreal, Que., Canada  
 Dr. Harold H. Jones, Winfield, Kans.  
 Dr. Edward L. Bortz, Philadelphia, Pa.

The Committee further places in nomination for election as Regent for a term expiring in 1951 the name of:

Dr. Wallace M. Yater, Washington, D. C.

The election of these Regents was moved by Dr. Maurice C. Pincoffs, and duly seconded.

President Fitz called for nominations from the floor; there being none, a motion was made, seconded and carried, instructing the Secretary to cast a single ballot for the election of all the above Regents.

DR. PINCOFFS (Continuing): The Committee places in nomination the names of the following men as Governors of the American College of Physicians for a term expiring in 1952:

Dr. Leland Hawkins, Los Angeles .....	CALIFORNIA (Southern)
Dr. Ward Darley, Denver .....	COLORADO
Dr. Thomas P. Murdock, Meriden .....	CONNECTICUT
Dr. John Minor, Washington .....	DISTRICT OF COLUMBIA
Dr. Cecil M. Jack, Decatur .....	ILLINOIS (Southern)
Dr. James O. Ritchey, Indianapolis .....	INDIANA
Dr. William C. Menninger, Topeka .....	KANSAS
Dr. Chester S. Keefer, Boston .....	MASSACHUSETTS
Dr. Joseph D. McCarthy, Omaha .....	NEBRASKA
Dr. Edward C. Reifenstein, Sr., Syracuse...	NEW YORK (Western)
Dr. Wann Langston, Oklahoma City .....	OKLAHOMA
Dr. Thomas M. McMillan, Philadelphia ...	PENNSYLVANIA (Eastern)
Dr. Charles W. Morton, Pittsburgh .....	PENNSYLVANIA (Western)
Dr. Charles F. Morsman, Hot Springs ....	SOUTH DAKOTA
Dr. William C. Chaney, Memphis .....	TENNESSEE
Dr. Fuller B. Bailey, Salt Lake City .....	UTAH
Dr. Nils P. Larsen, Honolulu .....	HAWAII
Dr. Herbert K. Detweiler, Toronto .....	ONTARIO
Dr. Francisco de P. Miranda, Mexico City ..	MEXICO
Dr. Gilbert M. Stevenson, Ancon .....	REPUBLIC OF PANAMA and the CANAL ZONE

In addition, the Committee nominates as Governor for a term expiring in 1951:

Dr. Walter I. Werner, Albuquerque .....

The election of these Governors was moved by Dr. Maurice C. Pincoffs and duly seconded.

President Fitz called for nominations from the floor; there being none, a motion was made, seconded and carried, instructing the Secretary to cast a single ballot for the election of all the above Governors.

# ANNALS OF INTERNAL MEDICINE

VOLUME 31

SEPTEMBER, 1949

NUMBER 3

## PHEOCHROMOCYTOMA: DIAGNOSIS AND TREATMENT \*

By GEORGE F. CAHILL, M.D., and HENRY ARANOW, JR., M.D.,  
*New York, N. Y.*

PHEOCHROMOCYTOMAS are relatively rare tumors of the chromaffin sympathetic nerve tissue, usually producing epinephrine, and/or, norepinephrine and most often seen in the adrenal medulla or in one of the many areas where chromaffin tissue occurs.<sup>1, 2</sup> The usual symptoms produced by the tumor are the result of the secretion of an excess of epinephrine or some other allied pressor substance, either intermittently or continuously. The action of epinephrine is hemodynamic and metabolic. The hemodynamic changes have a short latent period, a dependence of the magnitude of response upon the dose, and a rapid return to normal. They are a constriction of the peripheral arterioles with elevation of the blood pressure followed by a rise in cardiac output. The chief metabolic changes are increases in blood sugar, blood lactic acid and basal metabolic rate. These excess secretions of a pressor substance, if only occasional, may have no other effect upon the individual, but if frequent or continuous, may show the subsequent effect seen with continuous elevation of the blood pressure. From this it would seem that the syndrome is sufficiently distressing and that the symptoms are so characteristic that the diagnosis would be apparent. In fact, however, many of these cases are seen and treated without the correct diagnosis or the discovery of the cause.

The symptoms first described and most characteristic of the syndrome are the attacks of paroxysmal hypertension. On the other hand persisting unremitting hypertension has been shown to occur with some tumors, either developing from the intermittent hypertension or being unremitting from the onset. Some tumors of pheochrome tissue, rarely in the abdomen or chest

\* Presented at the Thirtieth Annual Session of the American College of Physicians, March 29, 1949, New York, N. Y.

From the Departments of Urology and Medicine, Columbia-Presbyterian Medical Center, New York City.

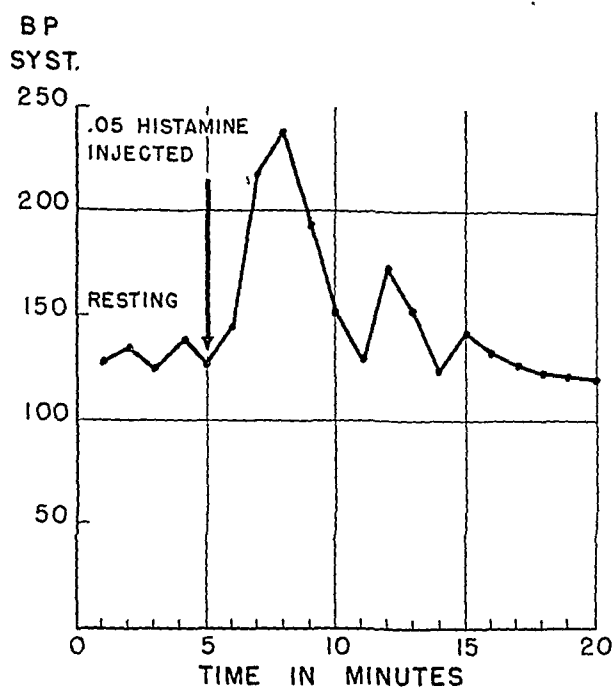


FIG. 3. Positive test in a case of pheochromocytoma with .05 mg. histamine base.

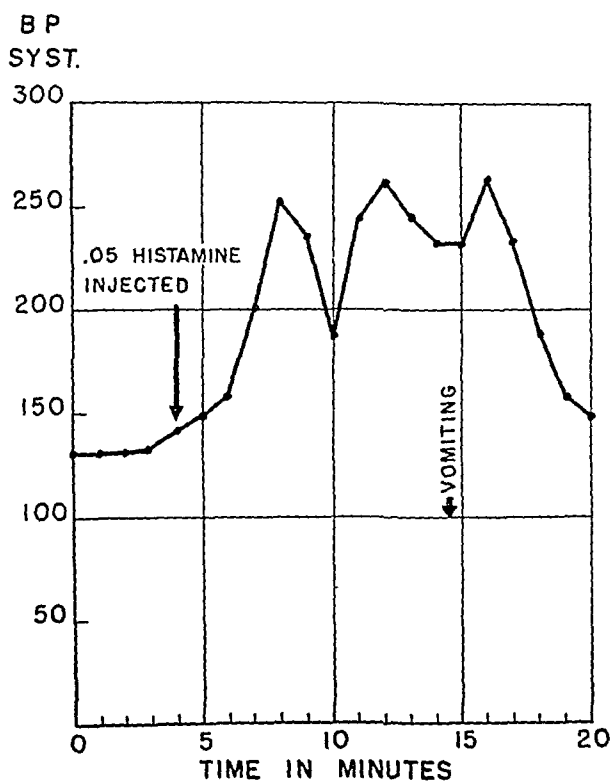


FIG. 4. False positive test with .05 mg. histamine base, in a case of psychoneurosis with hypertension. No tumor found on operative exploration.

the adrenals by air insufflation roentgen-rays. The operative explorations were performed to establish the diagnosis and in the hope of finding a tumor outside the adrenal and with atypical symptoms. A similar experience has been discussed by Van Epps et al.<sup>7</sup>. Rarely there appear in children, cases

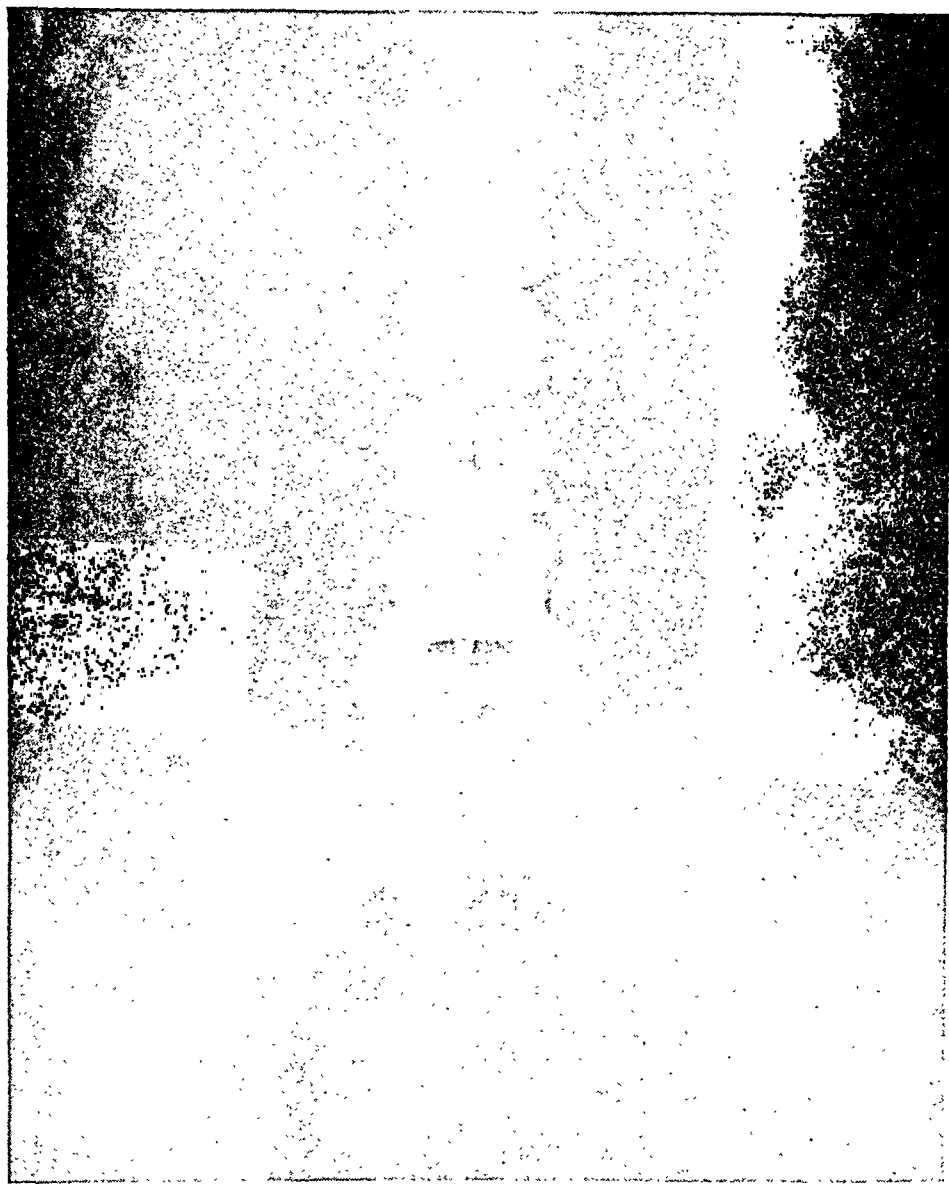


FIG. 5. Intravenous urogram showing iodide solution in the pelvis of the right kidney with a rounded tumor mass above the right kidney. The tumor mass was a pheochromocytoma.

with almost typical symptoms of paroxysmal crises, with associated metabolic changes and blood pressure changes suggestive of a positive reaction to benzodioxane, with no tumor disclosed either by roentgen-ray or by operation. These cases have resembled the case reported by Penfield<sup>8</sup> of tumor

Persistent hypertension with paroxysmal crises may occur. In Green's<sup>9</sup> review of 51 cases, 14 only showed intermittent hypertension and 37 had more or less continuous hypertension. Goldenberg et al.<sup>10</sup> quote Smithwick in which he found pheochromocytoma in 0.5 per cent of 1000 cases of hypertension subject to lumbo-dorsal sympathectomy. In any hypertensive that has paroxysmal crises, the possibility of a pheochromocytoma should be suspected, especially if any of the associated metabolic findings are present.

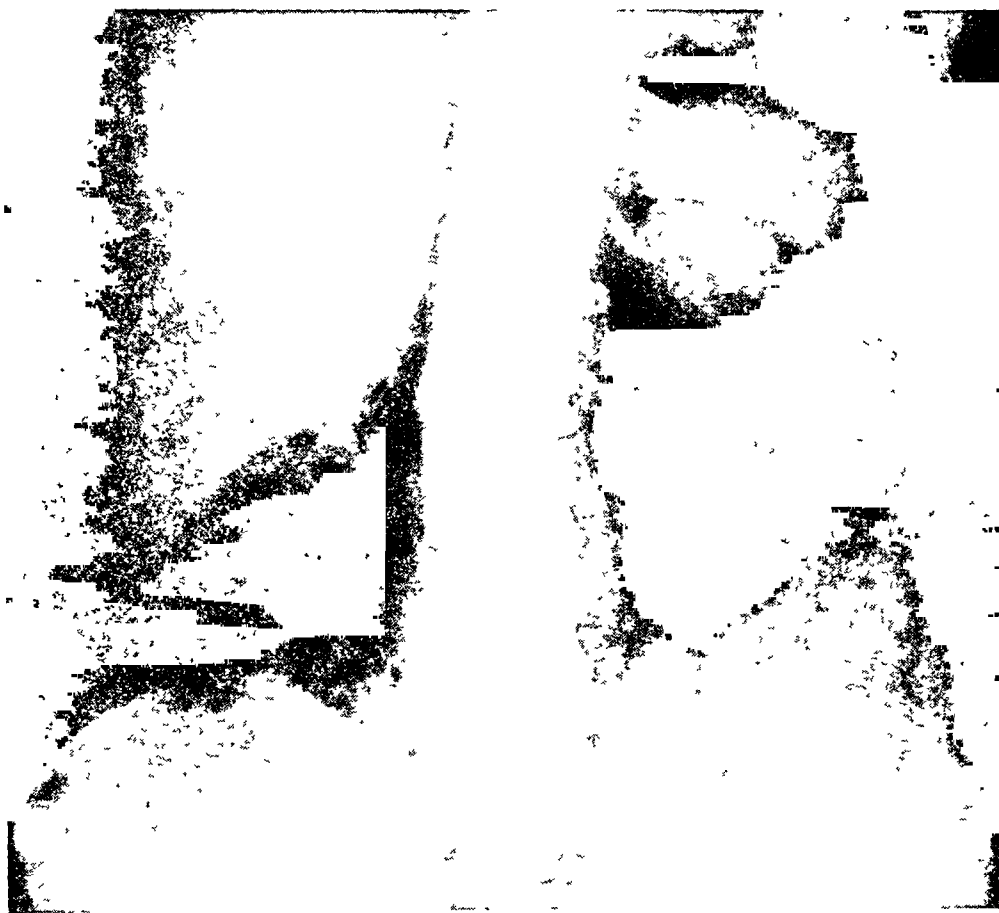


FIG. 7. Air insufflation roentgenograms with air in both adrenal fascial planes. The queer-shaped right area denser than normal proved to be only cortical tissue on a long ovoid cystic pheochromocytoma that filled the area also surrounded with air.

It is in this type of case that the use of epinephrine antagonists has proved helpful in the diagnosis.

The presence of permanent hypertension undistinguishable from essential or malignant hypertension in some of these cases has led Thorne<sup>11</sup> to suggest that each patient with severe hypertension be investigated for the presence of pheochromocytoma since removal of such a tumor gives one the opportunity of really curing a hypertension. Continuous unremitting hypertension has been reported with pheochromocytoma by Palmer and Castleman,<sup>12</sup>



cemias may often show extreme fluctuations. The glucose tolerance tests have marked variations but as a rule the tolerance is usually low. Thorn, Hindle and Sandmeyer<sup>22</sup> report in a tumor with persistent hypertension a glucose tolerance test that was high, the opposite to that usually seen. Clinically some of these cases may resemble the usual variety of diabetes as was shown by deVries et al.<sup>21</sup> Hypertensive crises with paroxysmal hyperglycemia and transitory glycosuria are not indicative of pheochromocytoma only, but may occur in other conditions.



FIG. 9. An air insufflation roentgenogram in a child with a large tumor between the vena cava and the aorta just below the liver. The air infiltrated around the left kidney which is normal but was unable to infiltrate on the right side. The air outlines the edge of the large tumor, just to the right of the vertebral column.

The effect of the excess epinephrine upon the glycogen from the liver may be shown by the estimation of the blood sugar and be of value in the diagnosis but the effect of the epinephrine upon the muscle tissue and the production of lactic acid with increase in the blood has not apparently been of use clinically for diagnostic purposes. Hypermetabolism can easily be shown to be present by the elevation of the basal metabolic rate. The ele-

specificity of these methods too has been questioned by the work reported by Kreuzfeldt.<sup>28</sup>

### USE OF EPINEPHRINE ANTAGONISTS

Of the large number of benzodioxanes first investigated by Fourineau and Bovet in 1935, two were selected by Goldenberg et al.<sup>29</sup> for study and for the purpose of devising a simple test to demonstrate the presence of excess epinephrine. Using 933 F and 1164 F, they were able to show that in doses ranging from 0.25 mg. to 0.43 mg. per kilogram of 933 F and three times as much of 1164 F, a purely adrenolytic action was obtained without any

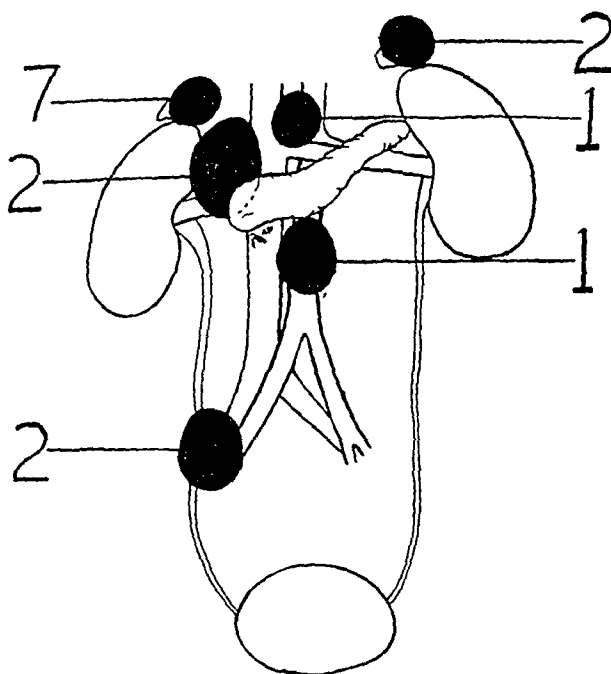


FIG. 11. A drawing showing the location of the pheochromocytomas occurring in the cases at the Presbyterian Hospital, New York City up to 1948, and the number in each situation. Three cases had multiple tumors, two in each case.

sympatholytic effects. After experimental work to show its safety in use, and its effect upon normal subjects, induced hypertensives, and in essential and renal hypertensives, they showed that a significant drop of blood pressure occurred in epinephrine induced hypertensives and in known pheochromocytomas during hypertensive states. They were able to conclude that it was of great aid for the diagnosis of excess circulating epinephrine. The action of these benzodioxanes was rapid and of short duration; the drop in blood pressure following the injection of 20 mg. of 933 F intravenously usually was of 10 to 15 minutes' duration. The use of this drug was described by them and by Cahill<sup>18</sup> in the diagnosis of tumors with persistent hypertension.

LaDue et al.<sup>29</sup> have recently reported that the intravenous injection of tetra-ethyl ammonium salts produces a paroxysmal elevation of the blood pressure in patients with pheochromocytoma and that this rise may be controlled by putting the patient in the upright position.

ROENTGENOGRAPHIC EVIDENCE OF THE PRESENCE OF A TUMOR EITHER  
WITHIN OR WITHOUT THE ADRENAL AS SHOWN WITHOUT OR WITH  
AIR INSUFFLATION OR BY RENAL DISPLACEMENT AS SHOWN  
WITH PYELOGRAPHIC MEDIA

The visualization of a tumor is a very important diagnostic procedure in chromaffin tumors. In some cases with a large tumor, a shadow may be present upon plain abdominal films and at times calcification in the tumor if present may bring out its shadow. Not infrequently, pyelography may show displacement of the kidney downward by the tumor mass and in some a flattening of the upper pole of the kidney when the tumor is within the adrenal. In the 18 cases studied by Howard and Barker,<sup>30</sup> 11 had the tumor diagnosed by pyelography. Perirenal insufflation has enabled us to establish the diagnosis when the tumor is within the adrenal.<sup>31</sup> The use of air insufflation in the localization of small tumors of the adrenal must be stressed because the site of such cannot be identified by any other method. Mencher,<sup>32</sup> Bauer and Belt<sup>4</sup> and we<sup>31</sup> have reported upon its value. When the tumor is without the adrenal there is difficulty in outlining it with air and of course recognizing where it is situated. In only one, a right lower ganglia tumor, were we able to show tumor without the adrenal by air insufflation. In several cases in which the tumors were in ganglia near the aorta and the fascial planes under pressure from tumor growth, the failure of air to infiltrate through those fascial planes suggested the site of the tumor.

When the tumor is intrathoracic the tumors have been clearly seen, as reported by Phillips<sup>14</sup> and in the unreported cases of Mayer<sup>33</sup> and Humphreys.<sup>34</sup> Here the lungs conveniently supply the contrasting air and the smooth outlines of these tumors have been clearly shown. Because of the possibility of intrathoracic tumor all cases should have such investigative films.

### TREATMENT

The treatment of pheochromocytoma is surgical removal of the tumor or tumors if more than one can be shown to be present. The operative mortality has shown a progressive reduction. It has been shown that surgical removal of the tumor or tumors completely relieves the patient of all the symptoms and signs of the suprarenal sympathetic syndrome.

A factor in successful operations upon these tumors is the planning of the procedure. If the use of dibenamine will condition the patient so that the danger of handling and releasing a fatal amount of epinephrine will be prevented, a valuable therapeutic aid has been presented. The toxic effects

- (a) History and findings.
- (b) Demonstration of excess pressor substance by an antagonist.
- (c) Demonstration, if necessary, of the production of excess pressor substance by a provocative.
- (d) Demonstration of the presence of a tumor by roentgen-ray.

4. The treatment is operative removal, the danger is during the operation.

5. If the patient survives the operative period, the pressure syndrome is cured and the ultimate prognosis is good because most of the tumors are benign.

#### BIBLIOGRAPHY

1. HOLTEN, P.: Noradrenaline in adrenal medullary tumors, *Nature*, 1949, clxiii, 217.
2. GOLDENBERG, M., FABER, M., ALSTON, E. J., and CHARGAFF, E. C.: Evidence of the occurrence of norepinephrine in the adrenal medulla, *Science*, 1949, cix, 534.
3. BEER, E., KING, F., and PRINZMETAL, M.: Pheochromocytoma with demonstration of a pressor substance in the blood, *Ann. Surg.*, 1937, cvi, 85.
4. BAUER, J., and BELT, E.: Paroxysmal hypertension with concomitant swelling of the thyroid due to pheochromocytoma of the right adrenal gland. Cure by surgical removal of the pheochromocytoma, *Jr. Clin. Endocrin.*, 1947, vii, 30.
5. ROWNTREE, L. G., and BALL, R. G.: Diseases of suprarenal glands, *Endocrinology*, 1933, xvii, 263.
6. WELLS, A. H., and BOMAN, P. G.: Clinical and pathological identity of pheochromocytoma, *Jr. Am. Med. Assoc.*, 1937, cix, 1177.
7. VAN EPPS, E. F., HYNDMAN, O. R., and GREENE, J. A.: Clinical manifestations of paroxysmal hypertension associated with a pheochromocytoma of adrenal. Report of proved and doubtful cases, *Arch. Int. Med.*, 1940, lxxv, 1123.
8. PENFIELD, W.: Diencephalic autonomic epilepsy, *Arch. Neurol. and Psychiat.*, 1929, xxii, 358.
9. GREEN, D. N.: Pheochromocytoma and chronic hypertension, *Jr. Am. Med. Assoc.*, 1946, cxxxi, 1260.
10. GOLDENBERG, M., SNYDER, C. H., and ARANOW, H.: New test for hypertension, *Jr. Am. Med. Assoc.*, 1947, cxxxv, 971.
11. THORN, G. W., HINDLE, J. A., and SANDMEYER, J. A.: Pheochromocytoma of the adrenal associated with persistent hypertension, *Ann. Int. Med.*, 1944, xxi, 122.
12. PALMER, R. S., and CASTLEMAN, R.: Paraganglioma (chromaffinoma, pheochromocytoma) of adrenal gland simulating malignant hypertension. Report of case, *New England Jr. Med.*, 1938, ccix, 793.
13. BINGER, N. W., and CRAIG, W. McK.: An atypical case of hypertension with tumor of the adrenal gland, *Proc. Staff Meet. Mayo Clin.*, 1938, xiii, 17.
14. PHILLIPS, R.: Intrathoracic pheochromocytoma, *Arch. Path.*, 1940, xxx, 916.
15. KIRSCHBAUM, J. D., and BALKIN, R. B.: Adrenalin-producing pheochromocytoma of the adrenal associated with hypertension. Report of three cases, *Ann. Surg.*, 1942, cxvi, 54.
16. McCULLAGH, E. P., and ENGEL, W. J.: Pheochromocytoma with hypermetabolism. Report of two cases, *Ann. Surg.*, 1942, cxvi, 61.
17. GANEM, E. J., and CAHILL, G. F.: Pheochromocytomas, coexisting in adrenal gland and retroperitoneal space with sustained hypertension, *New England Jr. Med.*, 1948, ccxxxviii, 692.
18. CAHILL, G. F.: Pheochromocytomas, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 180.

# THE PROGNOSIS AND TREATMENT OF HEPATIC INSUFFICIENCY \*

By CECIL JAMES WATSON, M.D., Ph.D., F.A.C.P., *Minneapolis, Minnesota*

THE term "hepatic insufficiency" may be defined according to the usage of the individual observer of hepatic disease. There would probably be a uniform acceptance of the term for the comatose or disoriented patient with a severe hepatic disorder, such as diffuse necrosis or cirrhosis. This is the way in which the term is most often employed. Probably the majority of observers would agree, however, that it might also be used to apply to more serious clinical states associated with diffuse parenchymal hepatic disease, with jaundice and/or ascites, but without obvious mental depression or aberration. It is doubtful whether anyone would consider the term applicable to such a disease as constitutional hepatic dysfunction or familial non-hemolytic jaundice; although this represents a mild selective form of hepatic insufficiency in which the liver cells are unable to transfer bilirubin to the bile as rapidly as it is formed. It would seem helpful to define the term "hepatic insufficiency" as that state in which the patient's normal economy and activity is seriously interfered with because of a diffuse hepatic injury; in other words, a state in which the functions of the liver are unable to meet the general needs of the individual. This definition is broader than that under which the term is usually employed; nevertheless, it appears to be in best agreement both with etymology and pathologic physiology, and it is therefore the definition which will be employed in the following discussion.

The prognosis and treatment of hepatic insufficiency are alike most difficult to evaluate. They are interdependent in considerable measure, and no attempt at strict separation will be made. Nothing could be more appropriate to this topic than the well known lines from Hippocrates' Book of Prognostics: <sup>1</sup> "He who would know correctly before hand those that will recover and those that will die, and in what cases the disease will be protracted for many days and in what cases for a shorter time, must be able to form a judgment from having made himself acquainted with all the symptoms and estimating their powers in comparison with one another." I am inclined to believe, however, that liver disease must have defied even the keen Hippocratic prognosis, and indeed we must freely admit that our ability to prognosticate or to treat liver disease on any rational basis, has made but tedious and small progress in the intervening centuries.

I will consider first the most important evidence of hepatic insufficiency. One should give due attention to the countenance and the behavior, again, quite in the Hippocratic tradition, <sup>1</sup> "If it be like those of persons in health,

\* Delivered in part as a morning lecture, Twenty-Ninth Annual Session, American College of Physicians, San Francisco, April 23, 1948.

From the Department of Medicine, University of Minnesota Hospital, Minneapolis, Minn. Aided by grants from the Dietene Corporation, Minneapolis, and the Medical Research Fund of the Graduate School, University of Minnesota.

those who are comatose and will eat nothing. Of crucial importance in all cases with anorexia is the *attention* given to the total food intake from day to day. All too frequently a sense of false security is gained merely by the fact that an adequate diet has been *ordered* or that certain amounts of glucose are being given intravenously, without due inquiry as to whether the 24 hour caloric intake has reached a desirable level. It is best that this be maintained on a *current* basis, not from week to week or even day to day, but from hour to hour. This requires a general awareness of the importance of the problem on the part of the attending physician, house officers, nurses, dietitians, and even the close members of the family, if intelligent and coöperative. It is well that the plan of dietary therapy be discussed at the outset and that frequent additional conferences be held to consider the necessity of changes. Insofar as current maintenance of intake is concerned it is desirable to replace promptly any deficits created by failure to eat the basic 2900 calorie diet as given above. It has been found advantageous in some cases to give small frequent feedings of an enriched \* milk mixture on an hourly schedule much as is done with a Sippy regime for ulcer. The total intake may then be calculated at 9 p.m., and if inadequate, may be supplemented during the night either by additional intravenous glucose or drip feeding of the enriched milk mixture through an indwelling nasal catheter. The latter should be given slowly, not more than one liter in six hours, and should be withheld in the presence of any tendency to regurgitation.

It is believed of value to administer glucose intravenously in any case of hepatic insufficiency in which anorexia is at all prominent, although the mere giving of intravenous glucose should not create the illusion that everything necessary is being done. From one to two liters of 5 to 10 per cent glucose, the amounts and concentrations commonly employed, provide but 200 to 800 calories, only a small fraction of the actual need. The exact amount and frequency of administration must depend upon individual factors. From one to two liters of 15 to 20 per cent glucose in distilled water, given at a rate of from 0.8 to 1.0 gm. per kilo per hour, provides 150 to 400 gm. of glucose, or 600 to 1600 additional calories. If given at a faster rate a significant loss in the urine must be anticipated. Should insulin be given with the glucose? Proof of its virtue in hepatic insufficiency has not been provided, nevertheless we are inclined to believe that it is beneficial at least in promoting appetite, in certain cases. If mixed directly with the intravenous solution, one unit per 3 or 4 grams of glucose, danger of hypoglycemia is largely removed.

The case described briefly in the following, illustrates the remarkable degree of recovery that may be noted in some instances of "alcoholic" cirrhosis, following a period of abstinence and correction of the dietary deficiency.

\* Our experience relates mainly to Meritene provided through the courtesy of the Dietene Corporation of Minneapolis. This is a calcium caseinate-skim milk powder-lactose combination which is readily mixed with milk, one part to six. For purposes of tube feeding the mixture should be prepared with a malted milk mixer or blender. It should be noted that this mixture produces a tendency to diarrhea in certain individuals.

of the severe evidence of liver cell injury at the outset, such as in case 1, above, is quite in accord with MacNider's view <sup>5</sup> that the resumption of normal function is due to a return to health on the part of individual cells. There is little doubt that a fatty cirrhosis, in which the enlargement is due mainly to fat rather than to adenomata and connective tissue, offers a much better prognosis than one of the latter type, even though it is still enlarged. The late stage of the disease with marked shrinking and great reduction in functioning hepatic parenchyma is usually beyond help. The simple removal of fat by means of lipotropic agents, is not necessarily attended by improvement, in fact cases have been observed in which a large fatty cirrhotic liver has been observed to diminish steadily under dietary and glucose therapy,

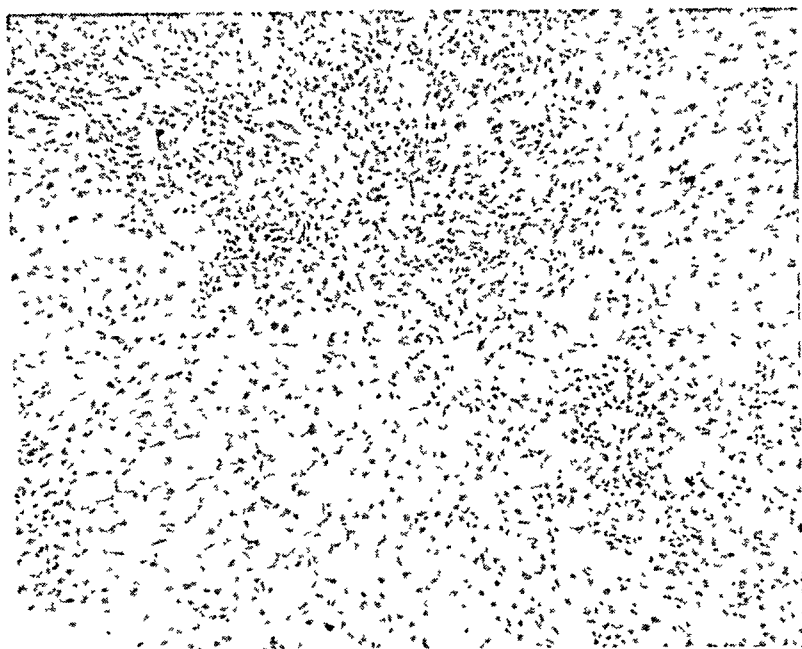


FIG. 2. Histologic appearance of liver biopsy from case 1 (August 20, 1945). Hematoxylin and eosin,  $\times 90$ .

yet with progressive hepatic insufficiency and at autopsy the finding of an atrophic or typical Laennec cirrhosis. Thus the prognosis probably depends on the amount of relatively normal liver parenchyma remaining at any given time, in other words what is left upon which dietary rehabilitation may be expected to exert a beneficial influence. It is evident, however, that this is not easy to assess. In case 1 the biopsy revealed a histologic picture which did not augur well for the patient's recovery; nevertheless the hepatic insufficiency quite disappeared and the patient is working and feeling well at the present time; in fact there is little doubt that he could pass an insurance examination if he were inclined to be untruthful.

At least in the cases of more severe liver disease, prognosis rests on such insecure bases that we cannot deny a period of intensive dietary and glucose

rather surprising immediately after the intensive course of human albumin. For a time the prognosis appeared hopeless; yet within a few days after all of the albumin had been given and coincident with the period of intensive glucose and insulin therapy, a striking improvement occurred, jaundice and ascites rapidly abated, and the patient was shortly able to leave the hospital feeling immeasurably better.\* This case also illustrates the very real difficulty that is likely to be encountered in attempting to carry out controlled studies of the effect of any one therapeutic factor in patients with hepatic insufficiency. Thus one is frequently persuaded that to continue with a longer trial of but one substance or of one relatively limited therapeutic regime in the face of a worsening clinical state, is to deny the patient the possible benefit of other methods of therapy. In case 2 as just related, it is conceivable that the patient would have recovered slowly but just as well if she had been continued on the simple dietary treatment of the first period on through February 28. While the albumin in this case appeared to do more harm than good the possibility is considered that she might not have had such a favorable result from the large amounts of intravenous glucose, had her nitrogen balance not been favored immediately beforehand. Eckhardt and co-workers<sup>6</sup> have shown that human albumin given intravenously is metabolized rather completely giving rise to a markedly positive nitrogen balance; at the same time they found a lag of several days from the time of injection to the peak effect on metabolism. Thorn and his associates,<sup>7</sup> and more recently Patek and co-workers,<sup>8</sup> have shown quite clearly that salt poor albumin administered intravenously in patients with cirrhosis and ascites, is lost in considerable amount into the ascitic fluid. They are inclined to believe that this may be the principal reason why the material is so little effective; yet it does not adequately explain the lack of diuresis and the marked weight gain with increasing signs of hepatic insufficiency, in spite of an elevation of the serum albumin to 5.0 per cent, such as occurred in case 2. This rather paradoxical situation, which has been observed in other cases of cirrhosis as well, and has been discussed in more detail in a separate communication,<sup>26</sup> simply emphasizes our need of more information regarding water balance in liver disease.

It is doubtful that the intraheptol played any significant rôle in the diuresis and ensuing improvement which commenced prior to its administration in case 2.

Case 3, the salient features of which are given in the following, is of particular interest in that, while the patient's initial status did not appear to be as grave as either of the first two cases, there was no response to dietary, intraheptol, or methionine therapy.

*Case 3.* Male, 54. Contractor. October 2, 1946: Long-standing chronic alcoholism until three months ago; no history of dietary deficiency although meat intake has always been rather small. Jaundice, ascites. Liver markedly enlarged. Numerous

\* Seen again on May 25, 1948, she was feeling very well and the jaundice had now quite disappeared. This status was maintained as of August 15, 1949.



sional instances have been noted in which marked improvement has occurred after transitory episodes of this type.

In case 4, also an example of alcoholic cirrhosis, the factors of infection and secondary malnutrition in precipitating hepatic insufficiency appeared to be prominent. This case was described in a previous communication.<sup>15</sup>

*Case 4.* Male, 58. Chronic alcoholism; moderate obesity. September 22, 1941: Admitted in semi-stuporous state. Disoriented. Mild jaundice. Feter hepaticus. Right saphenous thrombophlebitis. Temperature 102.4° F. Blood culture negative. Markedly enlarged liver and spleen. No ascites. Urine urobilinogen:

9-26	9-27	10-1	10-12	10-16	10-22	12-29
++++	++++	82.1 mg.	67.0 mg.	++	++(34 mg.)	++++

Serum bilirubin:  $I' = 0.7$ ;  $T = 1.48$  (September 27, 1941). Serum proteins:  $T = 5.8$ ;  $A = 2.7$ ;  $G = 3.1$  (September 27, 1941). September 23 to 26: Fluids, glucose, fruit juices. *No protein or vitamins. Marked improvement*; oriented; appetite returning. September 26 to October 25: P 150, C 200, F 30. Yeast, liver extract, vitamins. Discharged in relatively good condition.

The above instance simply illustrates the difficulty in evaluating therapeutic measures or substances supposed to have peculiar merit in the treatment of hepatic insufficiency; since it is evident that the hepatic coma promptly disappeared with bed-rest, fluids, and glucose alone. The main improvement had occurred before the patient was given any proteins or other accessory food substances. Although a biopsy was not secured in this case, it may be assumed from the rapidity of his response and progressive improvement, that the liver was largely fatty and only mildly cirrhotic. In passing, the rather striking dissociation of impairment of liver functions may be remarked upon. The urine contained large amounts of urobilinogen but the serum bilirubin was only slightly elevated.

As between the fatty and non-fatty types of "hypertrophic" cirrhosis (using the term hypertrophic in the broad sense) the former quite clearly has the better prognosis, and as we have seen in the foregoing cases, striking improvement may occur even though extensive fibrosis and change in the hepatic architecture has taken place. In the cirrhosis and diffuse hepatic injuries which are primarily non-fatty and non-dietary in genesis, it is doubtful that dietary therapy is of nearly as great significance in prognosis or treatment. In fact the more one studies this group, the more one is inclined to the belief that the physician's principal rôle is that of protecting the patient against further insult such as may arise from exertion, fatigue, malnutrition or negative nitrogen balance, drugs or chemicals, anesthesia, or needless cholecystectomy or exploration of the common bile duct. Of the utmost importance in this regard is an awareness of the possibility of diffuse liver disease such as hepatitis or cirrhosis in the patient whose past history of colic or of known gall stones or biliary tract disease, suggests an extra- rather than an intra-hepatic cause of jaundice. Case 5 is illustrative of such a pitfall.

hepatitis. The patient recovered but approximately four months later became jaundiced again and this time succumbed to a diffuse hepatic necrosis which may well have been on the basis of homologous serum hepatitis acquired from the plasma given four months earlier.

At the time that the above described case 5 developed what was in all likelihood homologous serum jaundice, the final outcome still might have been avoided had he been put promptly to bed on a good diet instead of which he was allowed continued activity on a restricted diet and given drugs which were obviously intended to relieve an extrahepatic biliary obstruction. Later, when he was admitted to the hospital, a composite liver function study might well have indicated the gravity of his disease. There was marked hyperbilirubinemia and on one occasion the qualitative urine urobilinogen test was positive, but additional studies were not carried out. A careful investigation of the cholesterol and cholesterol esters, and of the qualitative and quantitative aspects of the serum proteins would have been very helpful, and if doubt had still existed a liver biopsy would have been less compromising than an exploration of the common duct under general anesthesia. This patient received methionine in considerable amounts postoperatively, together with glucose, amino acids, and repeated infusions of plasma, all to no avail.

In case 6, which is described in the following, the composite liver function study gave warning of a considerable degree of hepatic insufficiency. This patient, a housewife 30 years of age, had had a cholecystectomy in July 1946. Following the operation she had a wound abscess and was quite ill with considerable fever for a period of two weeks, during which she was given three blood transfusions from individual donors. At the end of this time the abscess was drained and the patient recovered uneventfully. Approximately three months later she became jaundiced again, without pain or fever, and the jaundice deepened progressively. It was believed that she had a common duct calculus and she was referred to the University Hospital for choledochostomy. Physical examination revealed a rather deep jaundice, the nutrition being quite well maintained. The patient was alert and intelligent and in no distress. Her appetite was fairly good. Fetor hepaticus was observed. The liver was palpable coming down about 3 cm. below the right costal margin in the mid-clavicular line. The spleen was not palpable. There was no edema or ascites. A composite liver function study is shown in figure 6. This profile was much more suggestive of a diffuse parenchymatous jaundice than a common duct stone, and operation was consequently deferred. The patient was treated conservatively with a "liver diet," but at the end of two weeks the jaundice had not subsided and liver biopsy was therefore determined upon. The liver was not large enough to warrant a direct, subcostal biopsy. Peritoneoscopy was not considered because of the probability of multiple adhesions secondary to the previous operation and wound abscess; therefore, at our request, Dr. Richard Varco made a small incision in the right upper quadrant under local anesthesia, visualized and palpated the liver and took a 1 cm. wedge for microscopic examination. This revealed the

bed rest and maintenance of caloric intake, she gradually improved and her jaundice slowly diminished. She was able to return home and has since resumed some of her activity, although she reports by letter that the jaundice has not entirely disappeared. It seems likely that this patient will have a permanent residual cirrhosis. It is believed that another operation in this case, in the face of the evidence of the liver damage noted in figures 7 and 8, would have invited disaster. The patient's prognosis is sufficiently serious as it is, but at least she is alive and much better than at the time of admission.

From the standpoint of improving the prognosis by avoidance of needless operations, one of the most well concealed pitfalls is the case of diffuse cirrhosis with mild jaundice who presents because of "pseudo" gall stone colics.

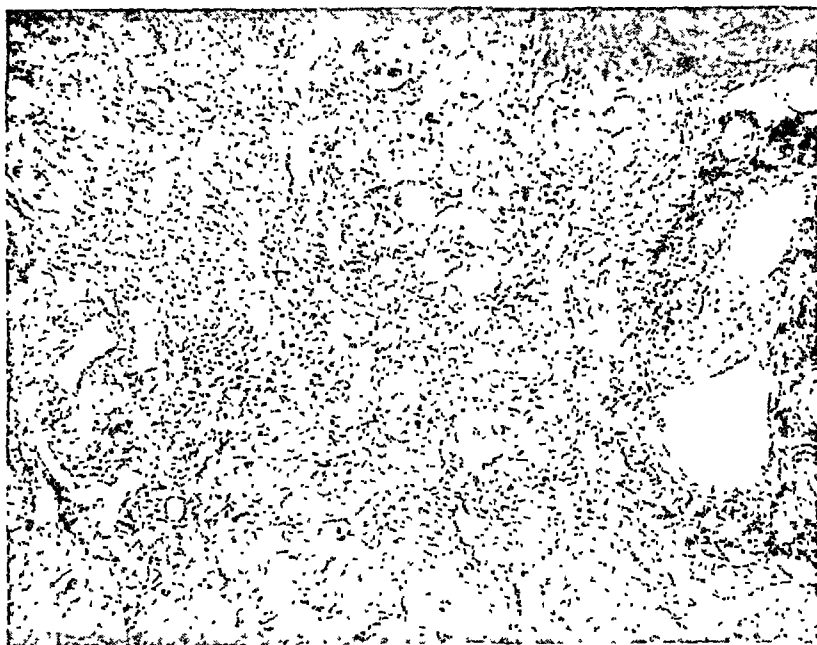


FIG. 8. Histologic appearance of liver biopsy from case 6. Mallory's connective tissue stain,  $\times 90$ .

This situation was well described many years ago by Naunyn<sup>19</sup> who recognized that typical biliary colics occurred in some non-calculous cases of cirrhosis. Our own experience includes at least half a dozen such instances the majority of which have had choledochostomy, fortunately without great harm, but also without benefit. In these the diagnosis of cirrhosis was not suspected preoperatively. It is possible that the composite liver function study will serve in the future, to put one on guard in such instances and that the method of cholangiography under peritoneoscopic control,\*<sup>20, 21</sup> may then

\* Since this was written we have attempted this method repeatedly, but with little success mainly due to difficulty in needling the gall-bladder. At present we prefer a small laparotomy under local anesthesia. This usually permits cholangiography on the table, as well as direct visualization of the liver and liver biopsy. If morphine and barbiturates are avoided the procedure is well tolerated and does not compromise the patient, unlike a choledochostomy.

apolis for a two month period, from April to June, 1947. Her jaundice gradually lessened, and she left the hospital about the middle of June considerably improved, although with distinct residual jaundice. During July 1947 she was up and about doing most of her own housework. On August 1 the jaundice deepened, the patient lost strength and appetite and was admitted to the University Hospital. In spite of the fact that the composite liver function studies (figure 9) strongly indicated a diffuse disease of the liver, either hepatitis or cirrhosis, or both, the question was raised as to the possibility of a common duct calculus or cancer, and in order to exclude this a peritoneoscopy and liver biopsy was done. The histologic appearance is noted in figure 10. The procedure appeared to be well tolerated, but about 36

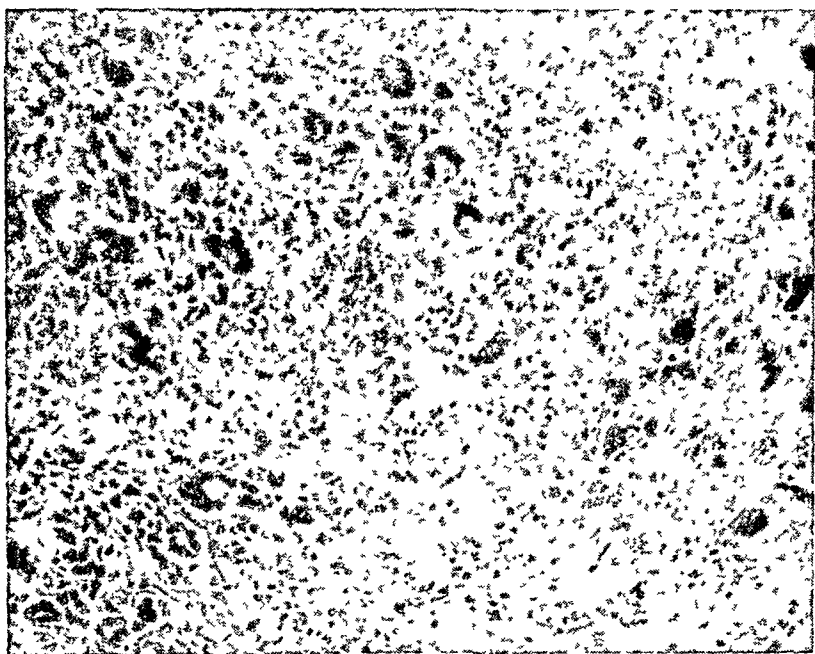


FIG. 11. Histologic appearance of liver obtained at necropsy in case 7. Hematoxylin and eosin,  $\times 150$ .

hours later the patient became disoriented and within another 12 hours was comatose. In spite of intensive therapy which included continuous drip feeding, large amounts of glucose, and 150 gm. of salt poor human albumin intravenously during a two day period, the course was rapidly downward. The liver dullness disappeared and the fetor hepaticus was outspoken. There was some ascites and increasing edema. At necropsy the liver weighed 1050 gm., and microscopically revealed extensive necrosis (figure 11) which had not been observed in the biopsy taken four days before death (figure 10). The brain showed areas of perivascular demyelination and endothelial proliferation, findings\* which are commonly encountered in patients dying of hepatic

\* Personal communication from Dr. A. B. Baker, Professor of Neurology, University of Minnesota.

tion of albumin is not without some danger from the standpoint of increasing the blood volume, embarrassing the myocardium, and producing pulmonary edema. Our experience in this regard has been reported in a separate communication.<sup>28</sup>

The dissociation of functional disturbance in cases of hepatic insufficiency is of much interest and deserves further comment. Fatal hepatic coma with little or no jaundice is not often observed but has been sufficiently well documented.<sup>23, a, b, c, d</sup> The following case is illustrative.

*Case 9.* Female, 69, housewife. Intermittent peptic ulcer symptoms for 40 years. Vomiting, hematemesis, melena for four days prior to hospital admission. Disorientation from fourth hospital day. Coma for last four days of life (fifth to ninth hospital days). Questionable slight jaundice on last day. No other significant findings. Composite liver function study as seen in figure 12. Necropsy: Advanced portal cirrhosis, liver wt. 1150 gm.; bleeding esophageal varices; benign chronic gastric and duodenal ulcers.

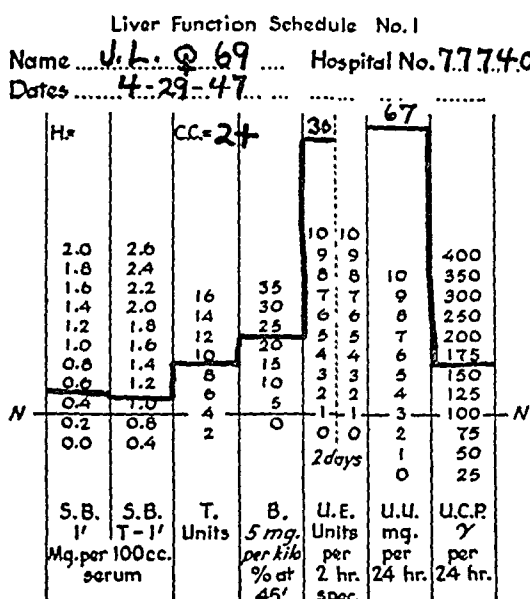


FIG. 12. Composite liver function study in case 9 (for key see caption to figure 1).

The large amounts of urobilinogen in the urine in case 9 indicated that bile was entering the intestine and by contrast with the serum bilirubin, that the liver excretory function for bilirubin was hardly impaired. This situation may be compared with the more usual one in severe hepatic insufficiency, i.e., that of marked hyper-bilirubinemia with a preponderance of 1' or prompt reacting serum bilirubin. This is of special interest with relation to the concept that the liver cells convert the delayed or indirect reacting bilirubin (globin) to the prompt reacting sodium bilirubinate and that the presence of the latter in the blood is an evidence of regurgitation of bile.<sup>24</sup> The finding of 30 or 40 mg. of prompt reacting bilirubin per 100 c.c. of blood shortly

- immunological studies on products of human plasma fractionation; use of salt-poor concentrated human serum albumin solution in treatment of hepatic cirrhosis, *Jr. Clin. Invest.*, 1946, xxv, 304.
8. PATEK, A. J., JR., MARKIN, H., COLCHER, H., LOWELL, A., and EARLE, D. P., JR.: The effects of intravenous injection of concentrated human serum albumin upon blood plasma, ascites, and renal functions in three patients with cirrhosis of the liver, *Jr. Clin. Invest.*, 1948, xxvi, 135.
  9. SCHUMM, O.: Hamatin als pathologischer Bestandteil des Blutes, *Ztschr. f. physiol. Chem.*, 1916, xcvi, 32.
  10. BINGOLD, K.: Blutstoffwechsel. *In: HIRSCHFELD, A., and HITTMAIR, A.: Handb. d. allg. Hamatol.*, Berlin, Urban and Schwarzenberg, 1, erste Hälfte, 601, 1932.
  11. VAN DEN BERGH, A. A. H., and KAMERLING, A. W. C. G.: Leverschirrhose met haemolytische anaemie en massale haematinaemie, *Nederl. Tijd. v. Geneesk.*, 1934, lxxviii, 4432.
  12. DUESBERG, R.: Über die biologischen Beziehungen des Hamoglobins zu Bilirubin und Hamatin bei normalen und pathologischen Zuständen des Menschen, *Arch. f. exper. Path. u. Pharm.*, 1934, clxxiv, 305.
  13. WATSON, C. J.: The pyrrol pigments with particular reference to normal and pathologic hemoglobin metabolism, *Downey's Handb. of Hematol.*, Paul Hoeber & Co., New York, 1938, iv, 2447.
  14. PASS, I. J., SCHWARTZ, S., and WATSON, C. J.: The conversion of hematin to bilirubin following intravenous administration in human subjects, *Jr. Clin. Invest.*, 1945, xxv, 283.
  15. WATSON, C. J.: Cirrhosis of the liver: Clinical aspects with particular reference to liver function tests. *Liver Symposium*, *Am. Jr. Clin. Path.*, 1944, xiv, 127.
  16. Homologous serum jaundice. Memorandum prepared by medical officers of the Ministry of Health, *Lancet*, 1943, i, 83.
  17. Catarrhal and human serum jaundice, Editorial, *Jr. Am. Med. Assoc.*, 1943, cxxii, 746.
  18. BARKER, M. H., and CAPPS, R. B.: Acute infectious hepatitis in the Mediterranean Theater, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 997.
  19. NAUNYN, D., Cited by UMBER, F.: Erkrankungen der Leber, der Gallenwege und der Pankreas, *Handb. d. inn. Med.*, Bd. III, Teil 2, 1926, J. Springer, Berlin, p. 100.
  20. ROYER, M., and SOLARI, A. V.: Cholangiography performed with the help of peritoneoscopy, *Gastroenterology*, 1947, viii, 586.
  21. HORAN, T.: Personal communication.
  22. FAGIN, D., and THOMPSON, F. M.: Cirrhosis of the liver, an analysis of 71 cases, *Ann. Int. Med.*, 1944, xxi, 285.
  23. (a) EPPINGER, H.: Die Leberkrankheiten. Allgemeine und spezielle Pathologie und Therapie der Leber, 1937, Julius Springer, Wien.  
 (b) WEIR, J. F.: Atrophy and necrosis of the liver without jaundice, *Ann. Int. Med.*, 1939, xii, 1845-1854.  
 (c) SATKE, O.: Acute atrophy of liver without icterus, *Wien. klin. Wchnschr.*, 1940, liii, 145.  
 (d) LAWRENCE, J. S.: Subacute necrosis of liver without icterus, *Lancet*, 1946, ii, 41.
  24. WATSON, C. J.: Some newer concepts of the natural derivatives of hemoglobin. I. General considerations. II. The serum bilirubin and bilirubinuria. III. The erythrocyte protoporphyrin, *Blood*, *Jr. Hematol.*, 1946, i, 99.
  25. ADAMSON, J. D.: The liver as the organ of sanguification, *Canad. Med. Assoc. Jr.*, 1928, xviii, 147.
  26. WATSON, C. J., and GREENBERG, A.: Certain effects of salt poor human albumin in cases of hepatic disease, *Am. Jr. Med. Sci.*, 1949, ccxvii, 651.

technic is not as effective for certain advanced psychotic states such as chronic schizophrenia as it is for depressions, obsessive-compulsive neuroses and other anxiety states. Freeman feels that this procedure is apt to be more effective when carried out under electric shock narcosis, instead of general anesthesia, and then followed by a course of electric shock treatments.

Brain operations for the relief of mental illnesses are not effective unless carried out in the frontal lobes, judging from unsuccessful results following occipital,<sup>15</sup> temporal,<sup>16</sup> and parietal lobotomies.<sup>17</sup> Moreover, experiences with cortical ablations involving subtotal removal of the cingulate gyri or the ventral surface<sup>12</sup> suggest that removal of these portions of the frontal lobes is not necessarily as important in the surgical improvement of mental disturbances as disconnection or removal of cortex in the region of areas 9, 10 and 46 of Brodmann. This is of interest in view of the work of Walker,<sup>18</sup> Legros Clark<sup>19</sup> and others, showing that areas 9, 10 and 46 are important stations for thalamic projections from the dorso-medial thalamic nuclei, and fits in with the theory that thalamo-cortical circuits may be of major importance in the manifestations and control of emotion or "affect." Interruption of these circuits is believed to benefit mental disturbances principally by reducing anxiety, tension and excess emotional charge. Such interruption may be accomplished at the cortical level by ablation (topectomy, gyrectomy); at the subcortical level by dividing white matter (various types of lobotomy); or at still deeper levels by destroying parts of the thalamic nuclei (thalamotomy).<sup>20</sup>

Experience with the various procedures just mentioned suggests that two factors are important in securing beneficial effects. One is quantitative; the degree or amount of nerve pathways interrupted must be *sufficient*. The second factor is qualitative: that is, the anatomical site of the lesion is important.

*Cortical Ablation:* As mentioned above, the first efforts to treat psychotic patients by cortical ablations were reported by Burckhardt in 1891.<sup>1</sup> In 1946, Heath and Pool<sup>10</sup> decided that limited cortical ablations confined to the prefrontal region of the brain might prove more specific and more satisfactory than prefrontal lobotomy, which up to that time had sometimes seemed a rather blind and uncertain procedure too often followed by unfortunate side-effects. Accordingly, a small series of subtotal ablations of cortex from the frontal lobes of psychotic patients was done<sup>10</sup> which later led to an extensive study of various types of cortical ablation conducted by the Columbia-Greystone Associates early in 1947.<sup>12</sup> This coöperative venture, together with further study by Pool, Heath and Weber,<sup>21, 22</sup> eventuated in the more or less standardized type of cortical ablation, *topectomy* (described below) which in turn closely resembles one type of cortical ablation (frontal gyrectomy) reported by Penfield in 1947.<sup>23</sup>

Topectomy (from *topos*, place; *ektos*, a cutting out) as currently practised is a topical type of cortical ablation limited to the rostromedial portion of each frontal lobe, as this seems to be an effective region for removal in

other conditions leading to severe anxiety; or depressed states with a suicidal trend. By far the largest group operated upon, because one of the most difficult to treat by any means, is the schizophrenic.

A psychiatrist, of course, must always select the cases for surgery and share not only in the choice of operative procedures but in the post-operative care.

*Results:* Really good results in the schizophrenic group following prefrontal lobotomy<sup>6</sup> or topectomy<sup>21, 22</sup> are obtained in about 20 per cent of the cases; fairly good results in another 20 per cent or more; and insignificant or poor results in the remainder. Most cases in the obsessive-compulsive group and the involutional type of depression are greatly improved by these procedures, while the psychopathic personality is least apt to be improved.

In the schizophrenic group the paranoid patient between the ages of 27 and 45 with at least some preservation of "drive" and will-to-get-better is most apt to improve. Results in manic-depressive or agitated and reactive depressive cases are, as a rule, less consistently good.

In summary, it appears that while we are apparently approaching a position where specific surgical procedures upon the brain may be selected for the relief of specific mental or emotional disturbances, much investigative work must be done before we can hope fully to understand the mechanisms and perfect the treatment of mental illness.

#### BIBLIOGRAPHY

1. BURCKHARDT, G.: Ueber Rindenexcisionen, als Beitrag zur operativen Therapie der Psychosen, *Allg. Ztschr. f. Psychiat.*, 1890-91, xlvii, 463-548.
2. MONIZ, E.: Prefrontal leucotomy in treatment of mental disorders, *Am. Jr. Psychiat.*, 1937, xciii, 1379.
3. FREEMAN, W., and WATTS, J. W.: *Psychosurgery*, 1942, C. C. Thomas, Springfield, Ill., p. 337.
4. LYERLY, J. G.: Transsection of the deep association fibers of the prefrontal lobes in certain mental disorders, *South. Surg.*, 1939, viii, 426.
5. SCARFF, J. E., and KALINOWSKY, L. B.: Prefrontal lobotomy under direct vision, *N. Y. State Jr. Med.*, 1947, xlvii, 2669.
6. POPPEN, J. L.: Technic of prefrontal lobotomy, *Jr. Neurosurg.*, 1948, v, 514.
7. HOFSTETTER, L., SMOLIK, E. A., and BUSCH, A. K.: Prefrontal lobotomy in treatment of chronic psychoses, with special reference to section of the orbital areas only, *Arch. Neurol. and Psychiat.*, 1945, liii, 125.
8. VAN WAGENEN, W. P.: Observations on changes in states of mental depression and tensions following surgical section of certain frontal lobe pathways, *Surgery*, 1946, xx, 656.
9. SCHWARTZ, H. G.: Personal communication.
10. HEATH, R. G., and POOL, J. L.: Bilateral fractional resection of frontal cortex for the treatment of psychoses. Preliminary report, *Jr. Nerv. and Ment. Dis.*, 1948, cvii, 411.
11. HEATH, R. G., and POOL, J. L.: Treatment of psychoses with bilateral ablation of a focal area of the frontal cortex, *Psychosom. Med.*, 1948, x, 254.
12. COLUMBIA-GREYSTONE ASSOCIATES: Correlative studies of the effects of ablation of different areas of frontal cortex in psychotic subjects, 1949, Paul B. Hoeber, Inc., New York, N. Y. (in press).



# STUDIES ON THE CORONARY CIRCULATION. VI. LOSS OF MYOCARDIAL CONTRACTILITY AFTER CORONARY ARTERY OCCLUSION \*

By MYRON PRINZMETAL, M.D., LOIS L. SCHWARTZ, M.D., ELIOT CORDAY,  
M.D., RAMON SPRITZLER, M.D., H. C. BERGMAN, Ph.D., and H. E.  
KRUGER, *Los Angeles, California*

## INTRODUCTION

It is well known clinically and experimentally that an ischemic portion of myocardium may bulge or "balloon" out during systole.<sup>1</sup> This remarkable phenomenon, which is of diagnostic and physiologic importance, has been very difficult to study in the past. Clinically, it has been observed on patients under the fluoroscope and may be graphically recorded by the electrokymogram and roentgenkymogram.<sup>2-8</sup> The information that can be obtained by such clinical procedures is relatively limited. At best, these clinical methods can tell us only whether bulging in systole is or is not present. It is highly probable that slight degrees of bulging may be overlooked altogether; and it has been reported that non-contractile regions may indeed be found in normal hearts.<sup>9</sup>

There have been great difficulties in studying this phenomenon in the experimental animal. This is because the heart beats so rapidly and the region of ballooning is so small that by ordinary observation it is difficult to be sure whether or not this phenomenon is present. The only systematic effort to study loss of myocardial contractility which we could find is the excellent work conducted by Tenant and Wiggers.<sup>1</sup> By means of a mechanical device placed over the bulging myocardium of the dog's heart, they recorded its motions and observed that the ischemic region ceases to contract within one minute after coronary artery occlusion.

It has been generally assumed that this loss of contractility of the ischemic myocardium is due to the accumulation of metabolites which prevent further contraction, analogous to the loss of function of a limb completely deprived of its blood supply.<sup>10</sup> This assumption is generally based on the erroneous idea that the coronary arteries are end arteries and that following coronary artery occlusion the ischemic myocardium is completely devoid of blood supply. In a series of experiments from this laboratory,<sup>11-14</sup> it has been demonstrated that the coronary arteries are not end arteries. Intercoronary anastomoses up to 200 micra in diameter have been found and shown to perform many vital functions<sup>13</sup>:

\* Presented at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 23, 1948.

From the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, California.

Aided by grants from the Blanche May and Beaumont Trust Funds.

When the artery was tied more proximally, i.e., close to its origin, ballooning of the ischemic myocardium was constant. However, when the tie was placed more distally from its origin, ballooning sometimes did not occur at all; if it did occur it was very slight and inconstant.

Slight ballooning, appearing early after coronary ligation, usually about 15 seconds after the artery was tied, could best be distinguished during systole, by noting an increase in the distance between two adjacent vessels on the epicardial surface of the ischemic myocardium. Prior to coronary artery

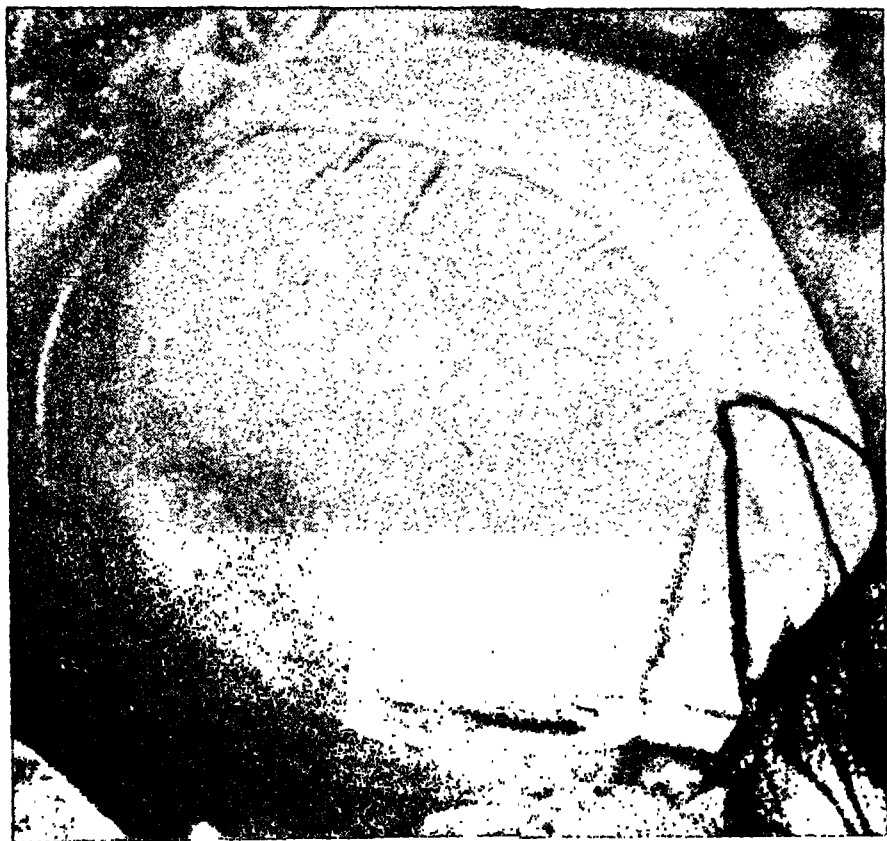


FIG. 1. Photograph of a dog's heart taken in full systole. The anterior descending artery has been ligated. The ischemic myocardium supplied by the ligated artery has ceased to contract and balloons outward in systole.

ligation, the distance between these vessels during systole remained unchanged or became less than it was during diastole. In figure 3, the gradual onset of ballooning after coronary ligation is illustrated. Single frames of motion picture film were projected by means of a still projector. From these projections, in which the heart was enlarged four times, tracings of the heart border and the surface vessels were made at the height of ventricular systole, before the artery was ligated, and 3, 5 and 10 seconds, respectively, after the artery was tied. These figures illustrate the gradual increase in distance be-

solely upon changes in the heart outline. Maximum ballooning involved a more extensive area of myocardium, and with its development the outline of the heart during systole was distorted. In addition, the ballooned region assumed a smooth globular appearance in contrast to the wrinkled undulated surface this area exhibited before the coronary artery was tied.

The surface area of myocardium involved in the ballooning even when it was most intense, generally appeared to be smaller than the portion of muscle supplied by the anterior descending branch of the left coronary artery. The reason for this is that anastomotic vessels now are nourishing the periphery of the affected area sufficiently to prevent loss of contractility and subsequent ballooning of these only partially ischemic portions of the involved myocardium.

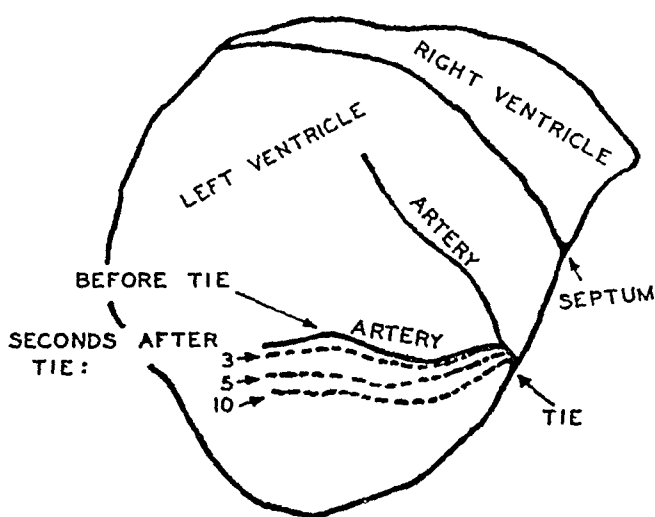


FIG. 3. Onset of ballooning. Tracings made from individual motion picture frames of the branches of the anterior descending coronary artery before, and 3, 5 and 10 seconds after, the ligation of the anterior descending coronary artery. The movement of the lower arterial branch is depicted by the dotted lines and reveals the increasing distance between the two branches caused by the ballooning of the ischemic myocardium.

The ischemic region of the right ventricle always contracted following the arterial tie. This again demonstrates a better collateral circulation to the right ventricle than to the left.<sup>18</sup>

*B. Late Systolic Ballooning of the Ischemic Region:* At the onset of ballooning, three to 10 seconds after coronary ligation, the ischemic region was generally observed to contract early in systole and balloon late in systole. This early systolic contraction and late systolic ballooning of the ischemic region persisted without progression or intensification throughout some of the experiments. In other experiments, however, the ballooning gradually became more intense until it occupied the whole of systole. Early systolic ballooning with late systolic contraction was never observed. This is demonstrated in figures 5 and 6, in which curves were constructed from measurements of the distance between the two adjacent vessels on the epicardial sur-

ments, after coronary ligation, it was observed that the central portion of the ischemic region exhibited marked ballooning throughout systole while the surrounding peripheral portion of ischemic myocardium contracted early in systole and ballooned slightly, late in systole. Such variations in non-contractility in the same heart are probably related to the degree of ischemia of the involved myocardium.

The simultaneous appearance of different types of ballooning in the same heart may well explain some of the bizarre roentgenkymograms which are otherwise difficult to interpret.

*D. Spontaneous Resumption of Contractility by the Non-Contractile Myocardium:* In the course of the preceding experiments it was frequently observed that ballooning disappeared and the non-contractile myocardium

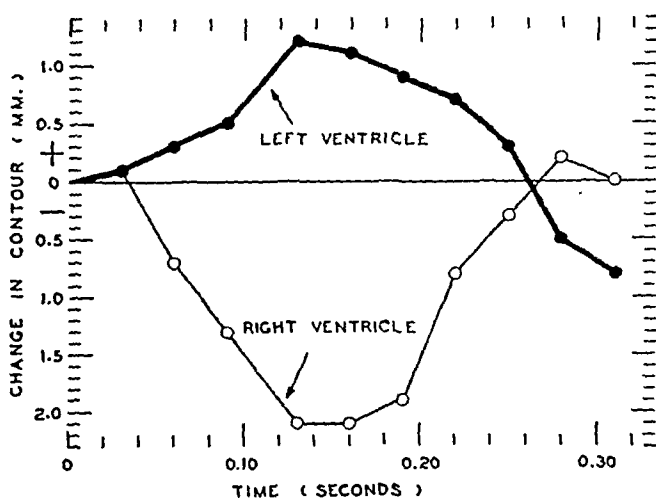


FIG. 6. Ballooning throughout systole. Change in contour of same heart as figure 5 during one complete cardiac cycle, 30 seconds after ligation of anterior descending branch of left coronary artery. Contour determined as in figures 5 and 6. Again the right ventricle contracts normally, but the left ventricle now balloons throughout systole.

spontaneously regained its contractility a few seconds later. In many instances in which well-marked ballooning was established, the contractions of the ischemic non-contractile region spontaneously reappeared, as long as 30 minutes after the ligation. For example, in one experiment, ballooning appeared 12 beats after the artery was ligated and then disappeared after 30 seconds. Two minutes later, however, the ballooning had reappeared, only to disappear again after 15 minutes. Thus, ballooning often waxes and wanes. The cause of this remarkable phenomenon of waxing and waning is not known. It may be due to variations in coronary blood flow produced by varying degrees of coronary spasm or to unknown neurogenic factors. It is of interest to note that we have observed similar waxing and waning of ballooning of the involved myocardium in human beings with coronary artery disease.

at the following times: (1) before coronary ligation, to show normal contraction; (2) 30 seconds after the arterial tie, to show marked ballooning; and (3) during the first beat following the compensatory pause, to show contraction of the ischemic region similar to that in the normal heart. Since the ischemic region which had spontaneously ceased to contract shortly after coronary occlusion definitely contracted at times in response to electrical

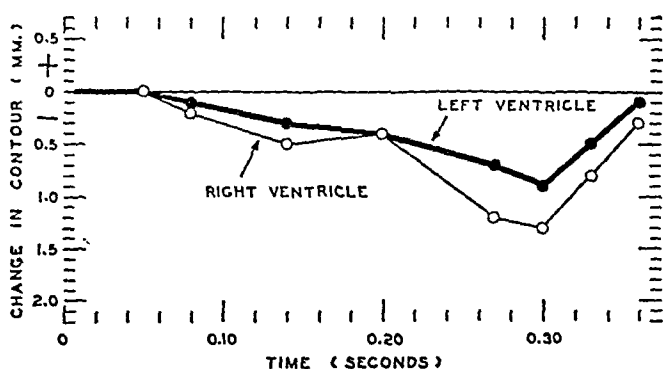


FIG. 7. Contraction of heart after compensatory pause following electrically induced extrasystole. Change in contour of same heart as previous three figures during part of compensatory pause and subsequent systole. Cycle is longer than normal due to initial compensatory pause. It can be seen that the left ventricle which ballooned in figure 6 now contracts similar to its contraction in figure 4 before the tie.

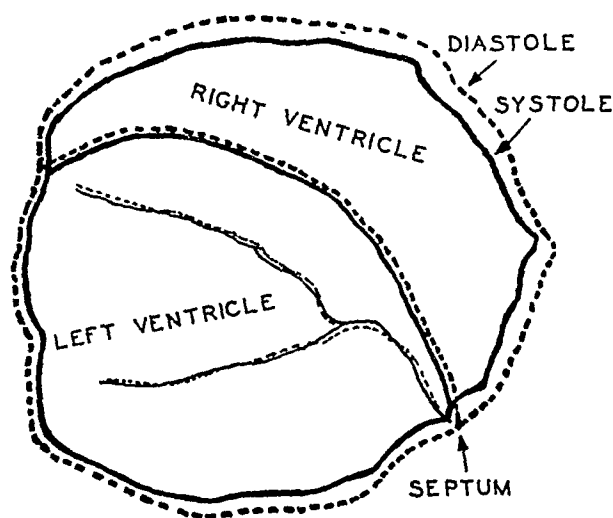


FIG. 8. Normal dog heart. Outline of the heart and anterior descending artery in maximum systole (solid line) and in diastole (interrupted line). The overall dimensions of the heart normally decrease in systole.

stimulation, and also contracted spontaneously during the first beat after the compensatory pause following ventricular extrasystole, it is concluded that this region *in situ* did not lose its ability to contract.

The fact that the ischemic, non-contractile region retains its ability to contract was further demonstrated by the following experiments in 11

### PART III. DEMONSTRATION THAT THE NON-CONTRACTILE REGION RETAINS CONDUCTIVITY

It has been suggested that the loss of contractility of the ischemic myocardium *in situ* is due to loss of the ability of this region to conduct the impulse for contraction. Harris and Matlock<sup>17</sup> found slowed myocardial conduction and diminished myocardial excitability in dogs with severe anoxia produced by the inhalation of gases with markedly reduced oxygen content. Drury<sup>18</sup> observed that increasing amounts of extreme pressure on an atrium of the dog's heart caused first a delay in conduction, leading sometimes to a two to one heart block, and finally complete interruption of conduction. Since this compression of the atrium causes, among other effects, diminution of the blood supply to the auricle, it appeared possible to explain this loss of conductivity on a basis of ischemia. Alteration or interruption of the conduction of the impulse to the ischemic region could therefore result in loss of contraction in this part.

In order to determine whether the non-contractile ischemic myocardium retained or lost its ability to conduct the impulse for contraction, the minimum strength of the electrical stimulus which was required to produce a ventricular extrasystole when applied to the ischemic region, was determined before and at various periods of time after ligation of the anterior descending branch of the left coronary artery in five dogs. By means of the

TABLE I

Dog No.	Time after Arterial Ligation (min.)	Minimum Stimulus Required for Extrasystoles*
707	- 2	L 3
	0	—
	1	L 3
	3	L 4
	4	L 4
	7	L 4
	19	L 4
712	- 2	L 3
	0	—
	5	L 3
	12	L 3
	17	L 3
714	- 2	L 3
	0	—
	1	L 3
	4	L 3
715	- 6	L 3
	0	—
	1	L 3
	6	L 3
	17	L 3
716	- 5	L 2
	0	—
	4	L 2
	5	L 2

\* Single break induction shock in arbitrary units, reading of Phipps and Bird Inductorium. Increased voltage is represented by increased numerical value (L 4 is greater than L 3, etc.).

Under conditions of extreme ischemia of cardiac muscle, when the muscle was cut out of the heart, we noted reduced conductivity. This is illustrated in table 2. In five of the experiments in Part II, in which the ischemic region was cut out of the heart, the strength of the electrical stimulus required to produce a contraction increased within 5 to 50 minutes. This was also true for the strength of the electrical stimulus required to produce a contraction in isolated portions of previously normal myocardium. The conditions of these experiments probably parallel more closely the conditions in the experiments described by Harris and Matlock.<sup>17</sup> It should be emphasized that impaired conductivity was found only in experiments in which pieces of myocardium were isolated and therefore entirely devoid of blood supply; in experiments performed *in situ*, probably because the ischemic myocardium received a collateral blood supply, no impairment of conductivity was observed.

#### PART IV. EFFECT OF INCREASED WORK ON BALLOONING

Patients with coronary artery disease, during their daily activity, must continually perform functions which increase the work of the heart, either by increasing blood pressure, cardiac output, or both.

In order to determine whether or not such increase of cardiac load has a deleterious effect on the contractility of ischemic myocardium, a coronary artery was partially tied in the distal third of its course to reduce its lumen. We have shown that little or no ballooning occurs in such a preparation if the blood pressure remains normal.<sup>14</sup> To increase the work of the ventricle, a large clamp was placed on the aorta, causing a marked narrowing of its lumen. This, of course, greatly increases the work of the left ventricle by raising the blood pressure to extremely high levels. It was found that if ballooning was not present before this procedure, it occurred during the increased work of the heart. If ballooning was present before the work of the heart was increased, the ballooning was greatly intensified during the acute hypertension. Obviously, loss of contractility has a deleterious effect upon the heart, because a large section of the myocardium loses its pumping function and thereby imposes an added burden upon the remaining contractile portions of the left ventricle. This experiment is a direct demonstration of the deleterious effect of increased work on the damaged heart. If the increased work is extreme, and the coronary arteries are diffusely diseased, it is easy to understand how death or heart failure may ensue. The importance of avoiding anything which increases the work of the heart in patients with coronary insufficiency is apparent.

In a previous communication<sup>14</sup> we have observed that decreasing the blood pressure by hemorrhage caused an increase in the ballooning. This is caused by marked diminution of the collateral circulation through the intercoronary anastomoses resulting from lowering of the pressure gradient. In the present experiment, however, raising of the blood pressure likewise

questionable diminished contractions in the involved region. A final film taken two months after the first again revealed systolic dilatation of a portion of the left ventricular border more marked than that observed in the original film. In addition it was noted in this film that in the center of the involved region dilatation occurred throughout systole, whereas at the periphery dilatation occurred only in late systole. Electrocardiographic changes first appeared on the sixth day and progressive changes occurred up to the twenty-fifth day, indicating posterior myocardial infarction. After the twenty-fifth day there were no further alterations in the electrocardiogram.

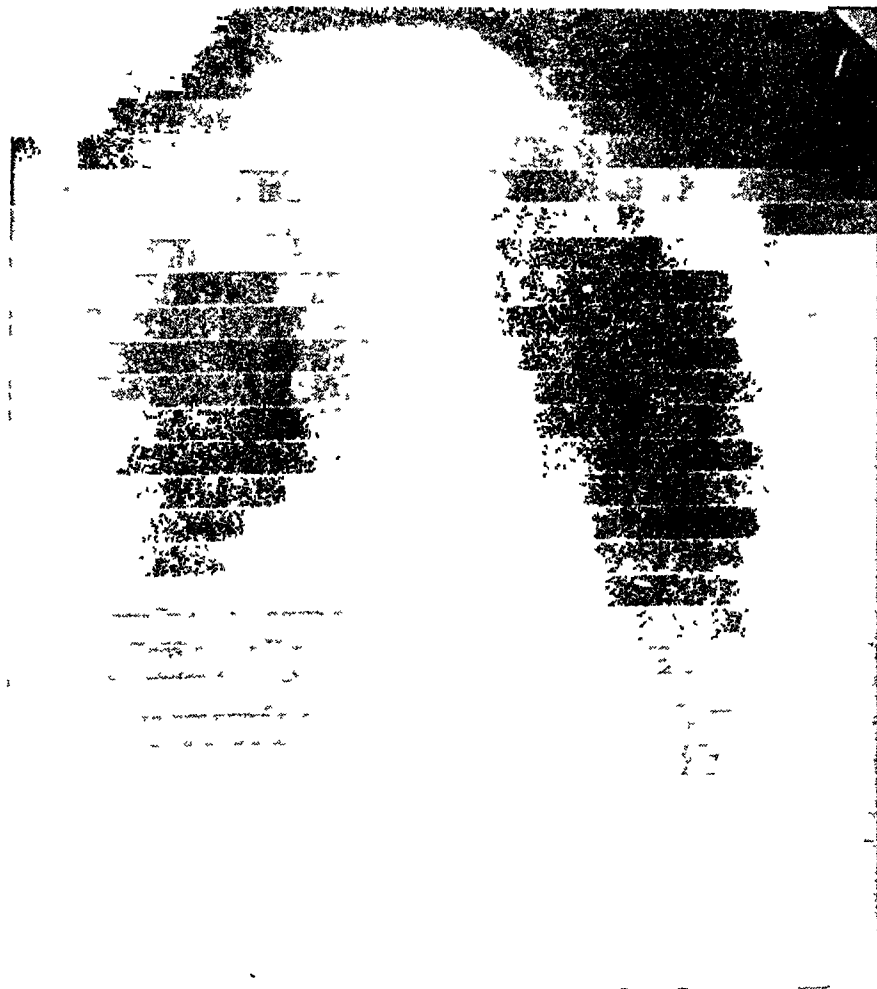


FIG. 11. Roentgenkymograms of patient taken two days after the onset of precordial pain. Note loss of contraction of left ventricle.

There was no correlation between the electrocardiographic changes and the alteration in myocardial contractility. This suggests that the electrocardiographic changes associated with myocardial infarction are not necessarily related to changes in contractility of ischemic myocardium.

The recovery of contractility in this case only one day after the onset of non-contractility presents further evidence that this recovery is not caused by retraction of the myocardium consequent to scar formation. The ob-



be of diagnostic importance. The absence of such changes, however, does not rule out coronary disease.

These observations will be extended, especially in cases of angina pectoris. It is believed that if diminution of myocardial contractility occurs during exercise-induced attacks of pain, such changes may be of diagnostic value in selected cases.\* These clinical observations confirm the experimental observations that myocardial non-contractility may be temporary and may be induced with increased heart work.

## DISCUSSION

Early in the course of our investigation, it was observed that ballooning did not always occur following coronary artery occlusion, and when it did it was often intermittent. This at first was difficult to understand, but after further investigation it was found that if the tie was made distally along the course of the artery so that only a small region of myocardium was ischemic, the myocardium often contracted normally and ballooning did not occur. It was reasoned that if the coronary arteries are end-arteries, ballooning of the ischemic myocardium would have resulted if its nutrient arteries were completely occluded. However, the ischemic region continued to contract. This is interpreted as complete proof that the coronary arteries are not end-arteries, physiologically. In the few instances in which ballooning did occur following a distal ligation it is possible that the pressure gradient of the interarterial anastomosis was reduced by the shock-like state produced by the surgical procedure. It was demonstrated in previous studies on shock that when the blood pressure was reduced, ballooning which was previously not present, or was slight, was intensified.<sup>14</sup> When a coronary artery was ligated near its origin, so that a large region of myocardium became ischemic, ballooning was a persistent phenomenon. This is explained by our previous studies on coronary anastomoses.<sup>14</sup> The region of ballooning was always found to be smaller than the region supplied by the coronary artery. This was because the blood entering by way of the collateral circulation enters the periphery so that the peripheral myocardium is more adequately nourished and therefore continues to contract. In ligations of intermediate sized arteries, ballooning often was an intermittent phenomenon, coming and going every few seconds. Undoubtedly sufficient blood intermittently entered the ischemic myocardium normally supplied by the occluded vessel to allow it to contract. This intermittency is also proof that the coronary arteries are not end-arteries.

These experiments were conducted in dogs in which coronary sclerosis was not previously present. It is well established that the intercoronary anastomoses are larger in humans in whom coronary sclerosis is present.

\* We have recently observed several patients with chest pain whom we examined fluoroscopically before and after exercise. It was found in some instances that non-contractility or systolic ballooning occurred after exercise which was not present before.

the "work" theory seems to be the most logical; however, at present we cannot reconcile all the evidence with such a theory.

Regardless of its mechanism, this phenomenon of cessation of contraction of the ischemic myocardium if limited in extent, may be considered protective in nature. Since the metabolic needs of contracting muscle are much greater than the needs of resting muscle, non-contractility of an ischemic region of myocardium would appear to be advantageous in preserving the damaged muscle.\* However, when the area of non-contractility is larger, the resulting hemodynamic changes may become a serious complicating factor. For example, when shock occurs following a coronary occlusion with its attendant drop in blood pressure, the blood supply to the myocardium not directly involved by the occlusion may be sufficiently embarrassed so that non-contractility becomes very extensive. Such a course of events might constitute a cause of sudden death following coronary occlusion clinically. This has been discussed more fully in previous studies.<sup>14</sup>

Patients with acute coronary occlusion frequently experience spontaneous disappearance and resumption of pain. Since ischemic myocardium does less work when it becomes non-contractile, possibly the spontaneous intermittency of contractility is related to the spontaneous intermittency of pain clinically.

The phenomenon of non-contractility with intermittent resumption of contractility noted in the experimentally induced ischemic myocardium in dogs was also observed in one patient with myocardial infarction of the posterior wall, and in one patient with angina pectoris after typical pain was induced by exercise. In the first case, the electrocardiographic changes did not appear to be correlated with the changes in contractility. There was evidence of loss of contractility in the first roentgenkymogram taken 36 hours after the onset of pain. The next roentgenkymogram showed resumption of contractility. Throughout this period the electrocardiogram remained normal. Because of our experimental observation in dogs that ballooning may appear and disappear following coronary artery occlusion, we made a definite diagnosis of coronary occlusion on this patient in the presence of a normal electrocardiogram. This diagnosis was confirmed by the development of typical electrocardiographic changes eight days later. In the patient with angina pectoris who developed loss of contractility after exercise the situation may be comparable to that of our dog experiments in which a coronary artery was ligated in the distal third of its course. In such a case no ballooning occurred until the work of the heart was greatly increased. It is possible that temporary loss of contractility may be a frequent occurrence in patients with coronary artery disease following exercise or increased work. If this be true, detection of such loss of contractility

\* We actually have no proof that the non-contractile muscle is "resting." It may be making a feeble effort to contract but this contraction is so weak that it is easily overcome by the systolic intraventricular pressure.

The authors wish to extend their sincere thanks to Miss Ethel Folodare, Edward M. Ornitz, Jr., Mrs. H. G. Liberty, Jr., and Mandel Silverbottom, Jr., for valuable aid in the conduction of this study; and to John R. Bishop and S. A. Sanford for their excellent work in motion picture photography.

## BIBLIOGRAPHY

1. TENANT, R., and WIGGERS, C. J.: The effect of coronary occlusion on myocardial contraction, *Am. Jr. Physiol.*, 1935, cxii, 351.
2. HIRSCH, I. S., and GUBNER, R.: Application of roentgenkymography to study of normal and abnormal physiology, *Am. Heart Jr.*, 1936, xii, 413.
3. GUBNER, R., and CRAWFORD, I. H.: Roentgenkymographic studies of myocardial infarction, *Am. Heart Jr.*, 1939, xviii, 8.
4. SUSSMAN, M. L., DACK, S., and MASTER, A. M.: The roentgenkymogram in myocardial infarction. I. The abnormalities in left ventricular contraction, *Am. Heart Jr.*, 1940, xix, 453.
5. DACK, S., SUSSMAN, M. L., and MASTER, A. M.: The roentgenkymogram in myocardial infarction. II. The clinical correlation, *Am. Heart Jr.*, 1940, xix, 464.
6. HENNY, G. C., and BOONE, B. R.: Electrokymograph for recording heart motion utilizing the roentgenscope, *Am. Jr. Roent. and Rad. Therapy*, 1945, liv, 217.
7. HENNY, G. C., BOONE, B. R., and CHAMBERLAIN, W. E.: Electrokymogram for recording heart motion, improved type, *Am. Jr. Roent. and Rad. Therapy*, 1947, lvii, 409.
8. LUISADA, A. A., FLEISCHNER, F. G., and RAPPAPORT, M.D.: Fluorocardiography: Technical aspects, *Am. Heart Jr.*, 1948, xxxv, 336.
9. GARLAND, L. H., and THOMAS, S. F.: Roentgen diagnosis of myocardial infarction, *Jr. Am. Med. Assoc.*, 1948, cxxxvii, 762.
10. LEWIS, T.: Pain in muscular ischemia, *Arch. Int. Med.*, 1932, xlix, 713.
11. PRINZMETAL, M., KAYLAND, S., MARGOLES, C., and TRAGERMAN, L. J.: A quantitative method for determining collateral coronary circulation, *Jr. Mt. Sinai Hosp.*, 1942, viii, 933.
12. PRINZMETAL, M., SIMKIN, B., BERGMAN, H. C., and KRUGER, H. E.: Studies on the coronary circulation. II. The collateral circulation of the normal heart by coronary perfusion with radioactive erythrocytes and glass spheres, *Am. Heart Jr.*, 1947, xxxiii, 420.
13. PRINZMETAL, M., BERGMAN, H. C., KRUGER, H. E., SCHWARTZ, LOIS L., SIMKIN, B., and SOBIN, S. S.: Studies on the coronary circulation. III. Collateral circulation of beating dogs' hearts with coronary occlusion, *Am. Heart Jr.*, 1948, xxxv, 689.
14. CORDAY, E., BERGMAN, H. C., SCHWARTZ, L. L., SPRITZLER, R. J., and PRINZMETAL, M.: Studies on the coronary circulation. IV. The effect of shock on the heart and its treatment, *Am. Heart Jr.*, 1949, xxxvii, 560.
15. LEWIS, T.: *Diseases of the heart*, 1934, MacMillan & Co., London.
16. GREGG, D. E., THORNTON, J. T., and MANTZ, F. R.: Phasic blood flow in coronary arteries, *Am. Jr. Physiol.*, 1939, cxxvii, 161.
17. HARRIS, A. S., and MATLOCK, W. P.: The effect of anoxemic anoxia upon conduction and excitability of mammalian cardiac muscle in situ, *Proc. Fed. Soc. Exper. Biol.*, 1947, vi, 123.
18. DRURY, A. N.: Further observations upon intra-auricular block produced by pressure or cooling, *Heart*, 1925, xii, 143.
19. SAMPSON, J. J.: Personal communication.
20. THOMAS, S. F., and GARLAND, L. H.: Roentgen cardiac diagnosis, *Calif. Med.*, 1948, lxxviii, 126.
21. WIGGERS, C. J.: *Physiology in health and disease*, 1944, Lea and Febiger, Philadelphia.

This generally consisted of three arteries posteriorly, one laterally, and one anteriorly about an inch to the left of the anterior descending branch. In one experiment, a large artery to the right of the anterior descending artery supplying the anterior aspect of the right ventricle was also ligated.

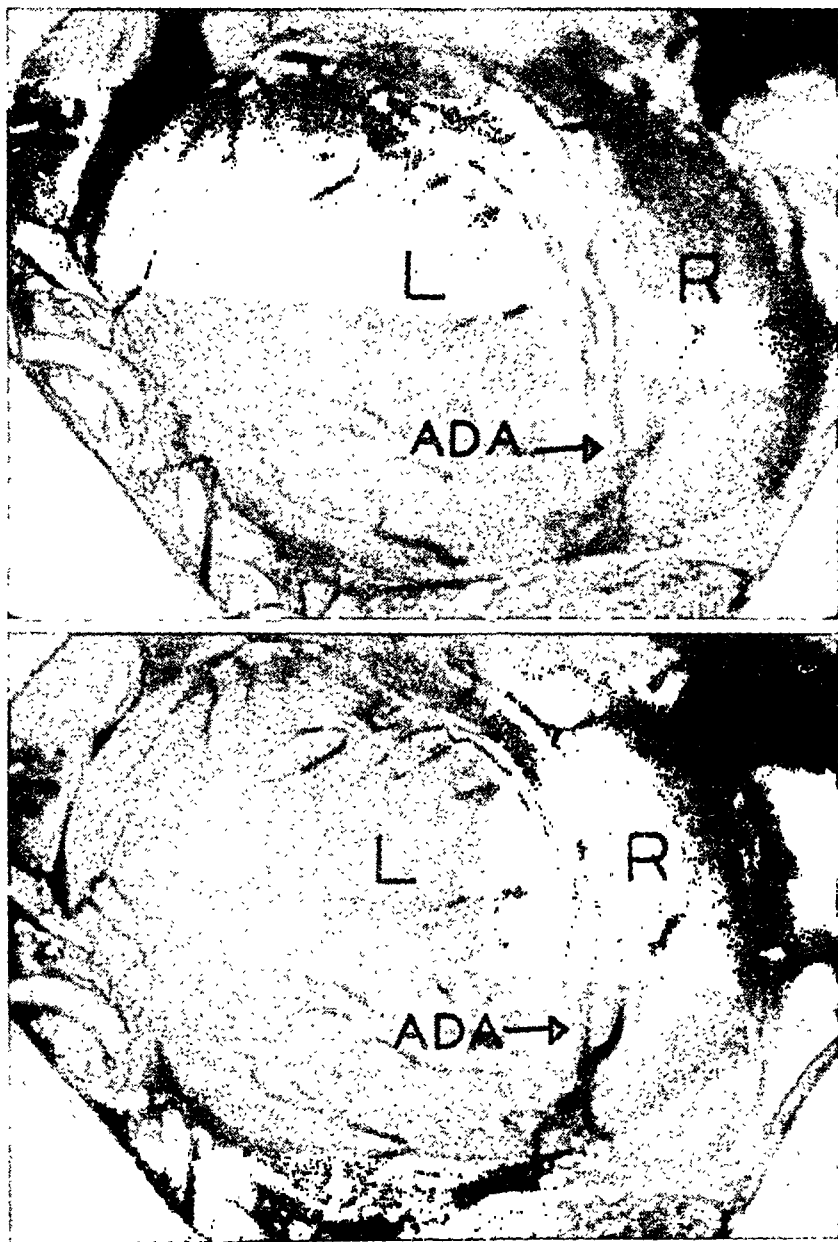


FIG. 1. All the major branches (seven) of the coronary arteries supplying the left ventricle have been ligated. Photographs taken 90 minutes after ligations. Blood pressure 120 mm. Hg. Note that the left ventricle balloons throughout systole and diastole. Approximately 15 per cent of the myocardium of the left ventricle (in the lower left corner) continues to contract and the rest balloons outward. *Above*, taken in full diastole; *below*, taken in full systole. L—left ventricle; R—right ventricle; ADA—anterior descending artery. This experiment can be demonstrated much more clearly in the motion picture.

ballooned out in systole. (In some experiments motion pictures were taken in such a manner that the posterior surface of the left ventricle could also be seen.) In some cases the heart continued to beat although only a small portion (approximately 15 per cent) of the left ventricle appeared to contract in systole. Yet, in none of these instances, in spite of the ligation of as many as eight arterial branches, was there a fall in blood pressure below the pre-ligation level; nor was there evidence of failure of the left ventricle, such as pulmonary edema, or dilatation of the right ventricle. Thus, this small segment of the left ventricle was able to perform in an apparently mechanically efficient manner the entire function of the left ventricle (figure 1).

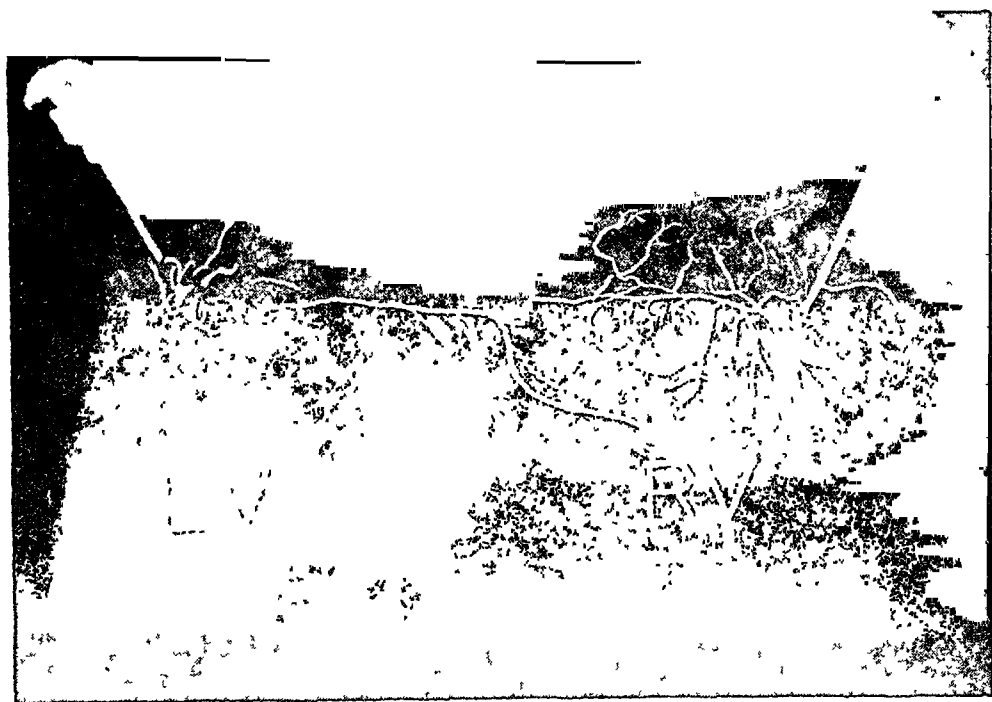


FIG. 3. Roentgen-ray of dog's heart with right and left coronary arteries injected with radiopaque material after ligation of all major coronary arteries of the left ventricle. Note the great diminution in number of patent arteries to the left ventricle. RV—right ventricle, LV—left ventricle.

In one experiment, after the mass ligation was completed, respiration suddenly ceased and asphyxia supervened. The usual asphyxial rise in blood pressure occurred; the mean blood pressure rose to over 200 mm. Hg. Thus, the remaining small segment of contracting left ventricle was able not only to maintain the circulation with normal blood pressure, but in an emergency, when the peripheral resistance was increased, successfully met the increased demand and elevated the blood pressure to almost double its normal value (figure 2).

In two experiments, the extent of the diminution in myocardial circulation after these mass ligations was demonstrated by intravenous injection of fluorescein in the manner previously described (by near ultraviolet light

number, may yet be sufficient to carry on a life-sustaining circulation. In the light of the experimental study described above, one muscle fiber in eight able to contract, may be sufficient to maintain life.

### SUMMARY AND CONCLUSIONS

1. In seven dogs all the major coronary arteries of the left ventricle were ligated. As many as eight coronary arterial branches were ligated in one animal.

2. By means of slow-motion colored pictures of these experiments, it was possible to evaluate the amount of myocardium that lost its power to contract. It was found that in dogs as little as 15 per cent of the ventricle apparently is sufficient to maintain adequate systemic circulation.

3. The greatly diminished blood supply to the myocardium, under the conditions of the experiments described above, was demonstrated by intravenous injection of fluorescein and motion pictures taken in ultraviolet light. It would appear that the Thebesian circulation supplied little or no blood under these circumstances.

4. In one experiment, the remaining contractile element was able to maintain an asphyxial rise of blood pressure from 100 to 200 mm. Hg.

5. These observations may offer a possible reason for the development of cardiac dilatation and hypertrophy in diffuse coronary artery disease even in the absence of hypertension. They may also suggest a possible explanation for survival in the presence of occlusion of both major coronary arteries, and for the persistence of life in spite of widespread disease of the myocardium.

The authors wish to thank John R. Bishop and S. A. Sanford for their excellent work in photographing the experiments; and Joseph Schanker, Anita June, and Eleanor Gerlach for technical aid in this study.

### BIBLIOGRAPHY

1. WRIGHT, SAMSON: Applied physiology, ed. 8, 1945, Oxford Medical Publications, New York, p. 879.
2. GOLDMAN, A.: Personal communication.
3. WRIGHT, SAMSON: Applied physiology, ed. 8, 1945, Oxford Medical Publications, New York, p. 746.
4. BEST, C. H. and TAYLOR, N. B.: Physiological basis for medical practice, ed. 4, 1945, Williams and Wilkins, Baltimore, p. 692.
5. GERMAN, J. K., BROWN, H. M., FOSTER, R. T., and GRISSEL, T. L.: Massive resection of the intestine, Jr. Am. Med. Assoc., 1947, cxxxv, 918.
6. PRINZMETAL, M., et al.: Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion, Ann. Int. Med., 1949, xxxi, 429-449.
7. PRINZMETAL, M., et al.: Studies on the coronary circulation. III. Collateral circulation of beating human and dog hearts with coronary occlusion, Am. Heart Jr., 1948, xxxv, 689.
8. PRINZMETAL, M., et al.: Studies on the coronary circulation. IV. The effect of shock on the heart and its treatment, Am. Heart Jr., to be published.
9. THOMAS, S. F., and GARLAND, L. H.: Roentgen cardiac diagnosis, Calif. Med., 1948, lxxviii, 126.
10. LEARY, T., and WEARN, J. T.: Two cases of complete occlusion of both coronary orifices, Am. Heart Jr., 1929, v, 412.

ing to the Pardee criteria.<sup>1</sup> The conventional limb leads, CF<sub>2</sub>, CF<sub>3</sub>, CF<sub>5</sub>, and aVR, aVL, and aVF<sup>2</sup> were obtained. Of these 168 electrocardiograms 134 had a Q wave in aVF, the size varying from 0.5 mm. to 8.75 mm. (table 1). Fifty-nine of the 168 electrocardiograms were obtained from 34 patients with a diagnosis of posterior myocardial infarction. The size and duration

TABLE I  
Size of QaVf in 168 Records

mm.	No.
0 to less than 0.5	34
0.5	10
1.0	22
1.5	15
2.0	17
2.5	14
3.0	14
3.5	3
4.0	8
4.5 to 8.75	31

of QaVF were measured (table 3); its percentage of QRSaVF was determined and these findings were correlated with the form of TaVF (table 2).

Examining these electrocardiograms for Goldberger's three criteria of posterior infarction in the unipolar extremity leads,<sup>3</sup> it is found (table 2) that 45 of the 59 electrocardiograms had a QaVF of 40 per cent or more of the QRSaVF; 35 had a QaVF of 0.04 second or more. In 43 TaVF was in-

TABLE II  
Correlation of QaVf Percentage and Time with Form of TaVf

	With TaVf Wave				
	Inverted	Diphasic	Flat	Upright	Total
QaVf 40% or more of QRSaVf (45) {with dura- tion of Q {0.04 second or more less than 0.04 second could not be measured	18	1	1	10	30
	9	0	0	0	9
	5	0	0	1	6
Total	32	1	1	11	45
QaVf less than 40% QRSaVf (11) {with dura- tion of Q {0.04 second or more less than 0.04 second could not be measured	2	2	0	1	5
	3	0	0	2	5
	1	0	0	0	1
Total	6	2	0	3	11
No QaVf (3)	1	1	0	1	3
Total 59	39	4	1	15	59

verted or diphasic. A Q wave of 40 per cent or more of the QRS and accompanied by an abnormal T occurred 34 times. A combination of all three criteria occurred only 19 times and was absent in 40. If, from this last group, we subtract the cases with QS and W complexes in Lead aVF as recommended by Goldberger, we would have remaining only 13 electrocardiograms which have all the criteria suggested by this author, thus failing

TABLE V  
Seventeen Non-Cardiac Cases with a Large  $Q_3$  as the Only Abnormality

Number.....	1	2	3	4	5	6	7	8	9	10	11	12	13	14*	15	16	17	Total
QaVf 40% or more QRSaVf														+				1
QaVf 0.04 second or more																		0
Form of TaVf (inverted, diphasic or isoelectric)									+			+	+					3
Chiefly due to QaVf								+										1
Chiefly due to RaVf	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	16

Note: \*QSaVF present.

unipolar leads were studied in these groups to see if they could help in deciding whether the  $Q_3$  was due to pathological changes in the heart or should be considered physiological (tables 4 and 5).

In the 12 records from patients with clinical heart disease (table 4) :

- A. Three had a QaVF of 40 per cent or more of QRSaVF (cases 2, 7, 12)
- B. Three had a QaVF of 0.04 second or more (cases 2, 7, 12)
- C. Five had a TaVF which was inverted, diphasic or isoelectric (cases 2, 3, 4, 10, 11)
- D. Three had A plus B (cases 2, 7, 12)
- E. One had A plus C (case 2)
- F. One had A plus B plus C (case 2)

In the 17 records from the cases without heart disease (table 5) :

- A. One had a QaVF of 40 per cent or more of QRSaVF (case 14)
- B. None had a QaVF of 0.04 second or more
- C. Three had a TaVF which was inverted, diphasic or isoelectric (cases 9, 12, 13)
- D. None had any combination of two or three of the above

In the 12 records from cardiac cases, criterion A was present three times and absent nine times. Criterion B was present three times in this group, actually in the same three records that showed criterion A. It was absent in nine records. Criterion C was found five times in the cardiac cases and was absent in seven records. The combination of A and B alone occurred three times and of A, B and C once. A and C, and B and C did not occur together except when all three criteria were present. In nine records, no combination of two or three criteria appeared. In the records from the non-cardiac cases (table 5), criterion A was found once. This record had a QS deflection in lead aVF, which Goldberger claims should exclude it from the supposedly significant category of Q greater than 40 per cent of QRSaVF. Accordingly its importance in determining the normal or abnormal significance of  $Q_3$  is nullified. Criterion C was found three times and the Q wave was never 0.04 second or more in duration. A combination of two or more



significance. This was not found to be the case, however, in our series. As is seen in table 3 the size of  $QaVF$  varied from 0 to 8.75 mm. and no matter what value was selected as the upper limit of normal we would still find a considerable number of cases below this limit. If we select 2.5 mm., we would find the value normal in 21 cases with posterior infarction; if we set it at 3.0 mm., we would find it normal in 28; at 3.5 mm., we would find it normal in 35; at 4.0 mm., we would find it normal in 38. The criterion that myocardial disease is indicated by a  $QaVF$  40 per cent or more of  $QRS aVF$  agrees with the clinical diagnosis as to normal or abnormal heart in 88 per cent of the complete series of 168 records. The criterion of  $QaVF$  25 per cent or more of  $RaVF$  agrees in 93 per cent. Therefore, the percentage method appears to be more useful than actual measurements.

### SUMMARY AND CONCLUSIONS

Goldberger's criterion that  $QaVF$  should have a value of 40 per cent or more of  $QRSaVF$  was only present in about 75 per cent of the records from cases with infarction. In almost 60 per cent  $QaVF$  had a duration of 0.4 second or more while about 70 per cent had an inverted or diphasic  $TaVF$ . A value for  $QaVF$  of 25 per cent or more of  $RaVF$  was present in 94 per cent of these records. On the other hand 98 per cent of the records afforded a positive diagnosis of infarction from the conventional limb Leads I, II and III. The unipolar leads were less useful and in no case afforded the only abnormal diagnostic feature.

The failure of  $QaVF$  to have the features considered significant of disease in so many of the records from patients with infarction makes it probable that it would be equally unreliable in determining the presence or absence of disease in those doubtful cases which have  $Q_3$  as the only abnormality of the electrocardiogram. This seems in fact to be the case since only 25 per cent of the group with a diagnosis of coronary arteriosclerosis showed the expected signs. It is difficult to appraise the significance of the one case supposedly without cardiac disease and yet showing  $QaVF$  more than 40 per cent of  $QRSaVF$  because this record had a small  $QS$  deflection in  $aVF$  and therefore might not have an abnormal significance.

It is apparent that criteria derived from the unipolar limb leads are not dependable in the diagnosis of posterior infarction. The conventional limb leads more often give a positive sign.

Unipolar limb leads are even more undependable in helping to recognize which records with large  $Q_3$  as the sole abnormality are derived from patients with coronary arteriosclerosis.

### BIBLIOGRAPHY

1. PARDEE, H. E. B.: Significance of electrocardiograms with large  $Q$  in Lead III, *Arch. Int. Med.*, 1930, xlvii, 470.
2. WILSON, F. N., et al.: Electrocardiograms that represent the potential variations of a single electrode, *Am. Heart Jr.*, 1933, ix, 447.

# IMMUNOLOGIC TYPES OF BLASTOMYCOSIS: A REPORT ON 40 CASES\*

By DAVID T. SMITH, M.D., F.A.C.P., *Durham, North Carolina*

ALTHOUGH sporadic cases of blastomycosis are found throughout the United States and Canada, the disease has been reported most frequently from the Mississippi Valley and the southeastern states. Durham, N. C. is near the center of the southeastern endemic area and over 50 cases have been studied in the Duke clinic in the past 18 years.

Approximately 45 per cent of the infections were confined to the skin, 45 per cent invaded the internal organs and, in 10 per cent, both the skin and internal organs were involved.

The prognosis seems to depend, at least in part, upon the immunologic status of the patient. Some patients develop humoral antibodies, which can be detected by the complement fixation test, and others acquire a hypersensitivity to the antigen of the organism as shown by the presence of a positive skin test either to a vaccine or to blastomycin.<sup>1</sup> The following combinations of immunologic reactions are theoretically possible and have been found, in approximately equal numbers, in a series of 40 cases: (1) skin test positive—complement fixation negative, (2) skin test positive—complement fixation positive, (3) skin test negative—complement fixation positive, and (4) skin test negative—complement fixation negative.

## SKIN TEST POSITIVE—COMPLEMENT FIXATION NEGATIVE

Patients with positive skin tests without complement fixing antibodies have the best prognosis (table 1). In cases belonging to this group, the infection was either a recent pulmonary invasion or a localized skin involvement. The disease apparently was not extensive enough to stimulate the production of humoral antibodies in amounts sufficient to be detected by the relatively insensitive method for complement fixation.<sup>2, 3</sup>

The good results obtained in this group may be explained by the limited degree of infection and the excellent resistance of the patient which was aided, perhaps, to some degree by the type of specific therapy. We learned, between 1930 and 1934, that patients who had positive skin tests to a *Blastomyces* vaccine either did not improve, or actually became rapidly worse, when iodides were administered.<sup>1</sup> Subsequently, it has been our practice to produce partial desensitization with a *Blastomyces* vaccine before adminis-

\* Presented at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 28, 1949.

From the Departments of Medicine and Bacteriology, Duke University School of Medicine, Durham, North Carolina.

The cost of this study was borne in part by a grant of the John and Mary Markle Foundation of New York.

ical recovery but the skin test, which had been depressed materially by the desensitization, gave a ++++ reaction 10 years after the disappearance of the complement fixing antibodies.

### SKIN TEST NEGATIVE—COMPLEMENT FIXATION POSITIVE

In this group of 10 patients (table 3) the skin tests were negative but complement fixing antibodies were present in titers ranging from 1:4 to 1:64. Physical examination revealed that all the patients had extensive generalized disease and all but two were obviously critically ill when first seen. The negative skin test is interpreted as the result of a terminal anergy analogous to that seen in patients dying of generalized tuberculosis. Martin<sup>5</sup> recognized this immunologic group in 1941 and emphasized the poor prognosis.

TABLE III  
Skin Test Negative—Complement Fixation Positive

Case	Skin Test	Complement Fixation	Type of Lesion	Clinical Condition	Results
1. C. C.	0	1:64	Generalized	Poor	Died
2. E. L.	0	1:32	Generalized	Poor	Died
3. S. D.	0	1:32	Generalized	Poor	Died
4. A. Y.	0	1:16	Generalized	Poor	Died
5. W. McN.	0	1:16	Generalized	Poor	Died
6. V. P.	0	1:16	Generalized	Poor	Died
7. W. E.	0	1:16	Skin—extensive	Good	Well—4 years
8. R. M.	0	1:16	Vertebrae	Good	Well—8 years
9. J. H.	0	1:4	Brain	Good	Died
10. T. C.	0	1:5	Generalized	Poor	Died

The two patients who recovered presented a clinical picture which was quite different from those who died. One patient, presented as case 7, had hundreds of primary skin lesions scattered over the entire body, without involvement of the internal organs and made a rapid and complete recovery following intensive therapy with potassium iodide. The patient, shown as case 8, had an extensive infection of 10 ribs and six thoracic vertebrae but no invasion of other tissues. A body cast was applied to support the weakened vertebrae and iodides were administered for a period of three years. Clinical improvement began in a few months but slow progression of the destructive lesions in the bones continued for four years. The patient is in excellent health after eight years, has no local symptoms, but still wears a partial body cast because the process of recalcification is not yet complete.

The death of eight out of 10 patients with negative skin tests and high titers of complement fixing antibodies is analogous to the results reported by C. E. Smith and his associates in California for cases of coccidioidomycosis.<sup>6</sup> In cases of progressive histoplasmosis the same phenomenon is frequently observed, although a few patients retain their sensitivity to histoplasmin. Among the five fatal cases reported by Bunnell and Furcolow,<sup>7</sup> two gave positive skin tests and three were negative.

ACTIVE IMMUNIZATION WITH *BLASTOMYCES* VACCINE

Pasteur's brilliant achievement of actively immunizing the patients with attenuated rabies virus, administered subsequent to infection but before the virus had reached the brain, has not been duplicated in any other disease. The essential requirements are: (1) a long incubation period between the time of infection and the time of dissemination and (2) a disease to which the patient can evolve a solid active immunity.

In 1941, a patient, listed as case 3, table 4, who had a rather extensive skin lesion, was treated intensively with a *Blastomyces* vaccine, roentgen-ray and potassium iodide. This patient made a satisfactory recovery and has remained well for the past eight years. It is not clear from our records why the vaccine was used and no attempt was made to ascertain if complement fixing antibodies developed subsequent to the administration of the vaccine.

In 1943, the patient, listed as case 2, table 4, was admitted to our hospital with a dense, circumscribed progressive lesion in the right upper lobe. The lobe was removed for carcinoma but the microscopic examination revealed the disease was blastomycosis. The lung was adherent to the chest wall in one area so some blastomycotic tissue was left in the chest. Large doses of potassium iodide were administered over the next six months to promote resolution and absorption of the residual lesion. The patient apparently was doing very well for six months and then developed a generalized infection of the bones and internal organs and died three months later. In reviewing this disastrous result it seemed that our therapy was ill chosen. By forcing the resolution of the granulomatous tissue with iodides, in an individual without humoral antibodies to the infecting agent, we may have accelerated unwittingly the process of dissemination.

In 1947, we studied another patient of this immunological type, case 6, where the entire lung had been removed for carcinoma in another clinic and later found to be blastomycosis. This patient had a residual lesion in one rib and a subcutaneous abscess which was discharging large numbers of *Blastomyces dermatitidis*. In this case, we attempted to immunize the patient with a heat killed vaccine made from her own organism before administering iodides.

The culture was grown on blood agar slants, suspended in physiological saline, measured by centrifugalization in a graduated centrifuge tube and then diluted with physiological saline to make a 1:1000 dilution by volume. The use of an autogenous culture is not essential since the studies of Conant, et al.<sup>11, 12</sup> have shown that all available strains of *Blastomyces dermatitidis* are immunologically identical.

The injections were given subcutaneously in doses of 0.2, 0.4, 0.8 and 1 c.c. every other day. The injections were discontinued for one week and then the patient's serum was examined for complement fixing antibodies. When no antibodies were found the course of the vaccine was repeated. One week after the second series of injections the serum was found to fix complement

those with negative skin tests and a high titer of complement fixing antibodies in their serum.

Patients having positive skin tests should be desensitized before being treated with iodides regardless of the presence or absence of antibodies.

Patients with neither positive skin tests nor complement fixing antibodies should be actively immunized with a heat killed vaccine made from the yeast phase of *Blastomyces dermatitidis* before being treated with iodides.

#### BIBLIOGRAPHY

1. MARTIN, D. S., and SMITH, D. T.: Blastomycosis. I. A review of literature. II. A report of thirteen new cases, *Am. Rev. Tuberc.*, 1939, xxxix, 275.
2. MARTIN, D. S.: Complement fixation in blastomycosis, *Jr. Infect. Dis.*, 1935, lvii, 291.
3. MARTIN, D. S., and SMITH, D. T.: The laboratory diagnosis of blastomycosis, *Jr. Lab. and Clin. Med.*, 1936, xxi, 1289.
4. HAMBLIN, E. C., BAKER, R. D., and MARTIN, D. S.: Blastomycosis of the female reproductive tract, *Am. Jr. Obst. and Gynec.*, 1935, xxx, 345.
5. MARTIN, D. S.: The application of immunologic principles to the diagnosis and treatment of certain fungus infections, *Jr. Invest. Dermat.*, 1941, iv, 471.
6. SMITH, C. E., WHITING, E. G., BAKER, E. E., ROSENBERGER, H. G., BEARD, R. R., and SAITO, M. T.: The use of coccidioidin, *Am. Rev. Tuberc.*, 1948, lvii, 330.
7. BUNNELL, I. L., and FURCOLOW, M. L.: A report on ten proven cases of histoplasmosis, *Pub. Health Rep.*, 1948, lxiii, 299.
8. MARTIN, D. S., and JONES, R. R., JR.: Systemic blastomycosis, *Surgery*, 1941, x, 939.
9. JONES, R. R., JR., and MARTIN, D. S.: Blastomycosis of bone, *Surgery*, 1941, x, 931.
10. HIATT, J. S., and MARTIN, D. S.: Recovery from pulmonary moniliasis, following serum therapy, *Jr. Am. Med. Assoc.*, 1946, xxx, 205.
11. CONANT, N. F.: Laboratory study of *Blastomyces dermatitidis*, Gilchrist and Stokes, 1898, *Proc. of Sixth Pacific Science Congress*, 1939, v, 853.
12. CONANT, N. F., MARTIN, D. S., SMITH, D. T., BAKER, R. D., and CALLOWAY, J. L.: *Manual of clinical mycology*, 1944, W. B. Saunders Co.

TABLE I

Case	Age	Illness Prior to SVCO*	Survival After SVCO*	Origin of Tumor	Method of Diagnosis	Microscopic Diagnosis
1	50	6 weeks	6 weeks	Rt. main bronchus	Autopsy	Squamous cell, grade IV
2	55	20 mos.	6 weeks	Rt. main bronchus	Autopsy	Completely undiff. (oat cell)
3	59	None	7 weeks	Rt. upper lobe	Biopsy cervical node	Completely undiff. (oat cell)
4	51	3 weeks	10 weeks	Rt. main bronchus	Bronchoscopic biopsy	Squamous cell, grade III
5	56	10 mos.	3 weeks	Rt. upper lobe	Biopsy cervical node	Undiff., grade IV
6	56	13 mos.	5.5 weeks	Rt. main bronchus	Bronchoscopic biopsy	Biopsy inadequate
7	48	10 mos.	3.5 weeks	Rt. main bronchus	Biopsy cervical node	Squamous cell, grade IV
8	42	3 weeks	12 weeks (living)	Rt. upper lobe	Biopsy cervical node	Moderately undiff.

\* Superior vena cava obstruction.

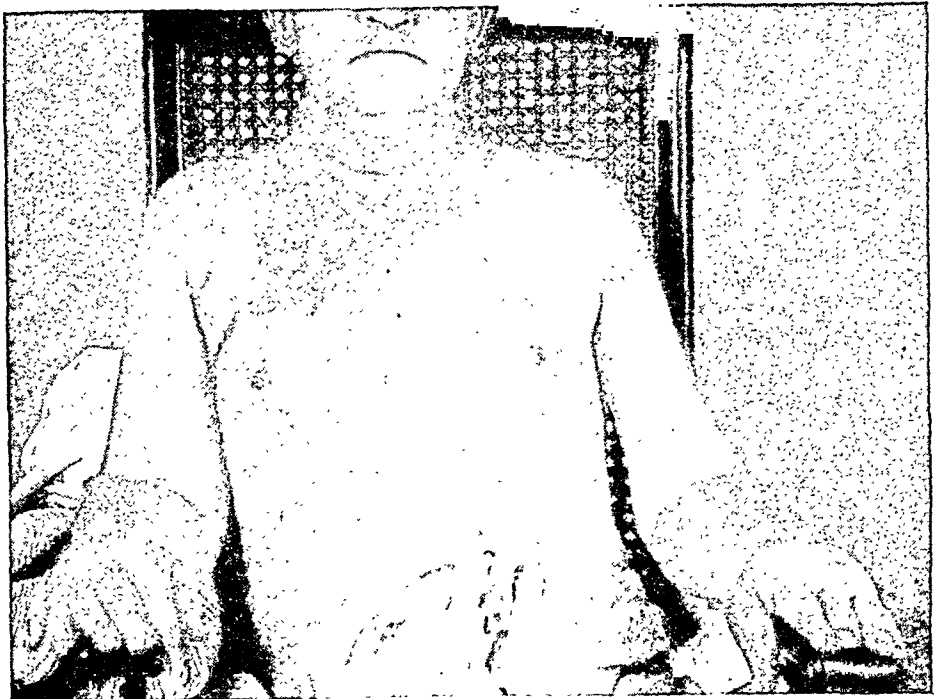


FIG. 1. Superior vena cava obstruction with edema of face, neck, chest, arms, and hands, and showing a plexus of venules across the lower chest.

In six cases, intensification of the cyanosis, dyspnea, and venous distention occurred in recumbency. Conversely, these patients felt better when sitting up.

Roentgen-ray examination of the chest revealed no characteristic picture. Two patients, however, displayed a widened superior mediastinal density compatible with a dilated superior vena cava. Phlebograms, obtained in two cases, revealed extensive collateral circulation, but the contrast medium failed to reveal the site of superior vena cava obstruction. Electrocardiographic findings were not significant.



FIG. 3. Phlebogram revealing extensive collateral circulation.

The primary lesion was in the right upper lung in all patients, and in four of these could be demonstrated in the right main bronchus.

The following pathologic findings were demonstrated in one of the autopsied cases:

A large firm tumor mass which originated in the right main bronchus filled the superior mediastinum. The azygos vein was obliterated, the su-

The signs and symptoms which develop following impairment of the venous return from this area vary with the degree of obstruction and with the presence or absence of occlusion of the azygos vein. Ochsner and Dixon<sup>6</sup> consider the following signs as pathognomonic of the superior vena cava syndrome:

- (1) Edema and cyanosis of the face, neck, and upper extremities
  - a. Aggravated by assuming the horizontal position
  - b. Relieved when erect
- (2) Venous hypertension in the arms
- (3) Normal venous pressure in the lower extremities
- (4) Development of subsequent varicosities of the anterior thorax

It is important to realize that the onset of superior vena cava obstruction may be the first manifestation of primary cancer of the lung. One of our patients experienced no symptoms referable to the respiratory system before the appearance of manifestations of superior vena cava obstruction. Early in the course, symptoms are likely to be slight, because of the development of a collateral circulation. Edema develops as the obstruction progresses. Edema of the eyelids may be an early sign of the syndrome.<sup>7</sup> Rauth<sup>8</sup> reported a fatality due to severe edema of the larynx.

Cyanosis is first observed in the lips and ear lobes and tends to progress. It is due to decreased oxygenation of tissues as a result of venous congestion.<sup>9</sup>

Dyspnea is a prominent symptom, occurs early, and may be attributed to retarded blood flow leading to venous stasis in the brain. Orthopnea, hyperventilation, paroxysmal dyspnea, or periodic breathing may also occur for the same reason.<sup>10</sup> Patients with preëxisting dyspnea due to the underlying bronchogenic carcinoma may exhibit a sudden increase of dyspnea with the appearance of superior vena cava obstruction. Cerebral symptoms, such as headache, fullness in the head and ears, dizziness, drowsiness, and mental lethargy are explained as due to dilatation of the cerebral veins with increased intracranial pressure and chronic congestion of the cerebral tissues.<sup>9</sup> The development of Jacksonian epilepsy in these patients has been noted.<sup>7</sup> The cerebrospinal fluid pressure may be increased,<sup>11</sup> as was demonstrated in one of our cases. Conjunctival suffusion and prominent, staring eyes may occur from increased cerebral pressure.<sup>12</sup> The fundal veins are likely to be distended.

Characteristically, most of the signs and symptoms are aggravated in recumbency as a result of increased venous stasis in this position.

As mentioned previously, the elevated venous pressure is manifested by dilated veins of the head, neck, chest, and arms. Small superficial groups of dilated venules may appear along the anterior costochondral margins and be the first evidence of superior vena cava obstruction. Their presence is an indication for a thorough examination of the chest.<sup>13</sup> As the collateral circulation becomes more extensive, venous distention appears in the lateral and posterior chest wall, and the upper and lower abdominal wall.



## SUMMARY

An analysis, together with a discussion of the findings, of eight cases of superior vena cava obstruction occurring as a complication of primary cancer of the lung has been presented. In all instances, the tumor originated in the right upper lobe. In seven of the eight cases, death occurred three to 10 weeks after the onset of obstructive manifestations.

Obstruction of the superior vena cava is an important and not infrequent complication of bronchogenic carcinoma and may be the first indication of this disease. The development of this complication is an ominous occurrence.

## ADDENDA

Case 8 died 14 weeks after the onset of symptoms of superior vena cava obstruction. Autopsy disclosed a tumor originating in the right main bronchus which invaded the wall of the superior vena cava, completely occluding its lumen, from the auricle to the subclavian vein. The azygos vein was similarly compressed.

Since the completion of the above report an additional case of superior vena cava syndrome secondary to bronchogenic carcinoma, has been observed. The patient was ill 10 weeks before the obstruction manifested itself. Death occurred five weeks later. Figure 4 clearly illustrates the extensive collateral circulation over the chest and abdomen which developed following obstruction. In contrast to the other eight cases, the



FIG. 4. Infra-red photograph taken four weeks after onset of superior vena cava obstruction demonstrating extensive collateral circulation over chest and abdomen.

# THE INCIDENCE OF HYPERTENSION IN PORTAL CIRRHOSIS: A STUDY OF 80 NECROPSIED CASES OF PORTAL CIRRHOSIS \*

By SAMUEL D. SPATT, M.D., and PHILIP ROSENBLATT, M.D.,  
*Brooklyn, New York*

It is the general impression of many physicians that hypertension occurs much less frequently in patients with portal cirrhosis than in the general population. This impression receives some support from the statement in Oxford Medicine <sup>1</sup> that "in portal cirrhosis, the pulse is slightly quickened, the blood pressure, both arterial and venous, usually is low," and the statement in the book by Rolleston and McNee <sup>2</sup> that "the blood pressure is low when the disease is active." However, there are not many references in the literature dealing specifically with the subject of hypertension in portal cirrhosis.

In 1943, Kirshbaum and Shure <sup>3</sup> stated, "There seems to be no indication that cirrhosis of the liver, per se, has any marked effect on the cardiovascular system." Another report by Bouchut et al. <sup>4</sup> resulted in similar conclusions.

There is no mention in these reports of the incidence of hypertension in the general population to which its incidence in portal cirrhosis must be compared. Moreover, the standards used for the diagnosis of portal cirrhosis in these studies were not mentioned and thus may differ from each other and from those used in the present series.

In view of the above, it seemed pertinent to investigate the incidence of hypertension in autopsied cases of portal cirrhosis at this hospital.

In an effort to standardize the cases used in this series and to prevent possible disagreement on the amount of microscopic pathology needed to establish the diagnosis of portal cirrhosis, all cases which did not show nodules or a "hob-nail" appearance grossly were discarded. Microscopically these cases also showed markedly increased periportal fibrosis, cellular infiltration of the periportal connective tissue, disorganization of liver lobules with disappearance or dislocation of central veins, regeneration of hepatic cells and an apparent increase in the number of bile ducts.

The first problem was to arrive at some conclusion as to the incidence of hypertension in the general population. This was difficult because of the different standards and various population and age groups used by various investigators. Some of these are given below.

Master et al. <sup>5</sup> studied 15,000 men and women over 40 years of age. Using various standards for hypertension, such as 140/90, 150/90 and 150/100 mm. Hg, the authors found hypertension present in a surprisingly large portion of the general population. For example, if 140/90 mm. Hg is

\* Received for publication March 11, 1948.

From the Department of Laboratories, Jewish Hospital of Brooklyn.

there was only one case of hypertension, so that among 60 cirrhotics above 40 years of age, there were 11 cases of hypertension (18 per cent).

In the table below the incidence of hypertension in the general population above 40 years of age as determined by Master et al.<sup>5</sup> is compared with that in the present series.

From the above table it may be seen that the incidence of hypertension is markedly less in our series. It may also be seen that the increasing incidence of hypertension with age occurs in our series as well as the other. The possible explanations of the difference in incidence of hypertension in the two groups will be discussed later.

If the weight of the heart is to be used as a criterion of hypertension, we have some difficulty again in establishing a standard. The generally accepted upper limit of normal weight of the heart is 300 gm. in females and 350 gm.

TABLE I

	Patients with hypertension in general population (Master et al. <sup>5</sup> )			Patients with hypertension in the present series of portal cirrhosis (Spat and Rosenblatt)
	Male	Female	Total*	Total
Age 40 and over	49.8%	59.8%	Over 50%	18%
Age 50 and over	59.9%	72.5%	Over 60%	21%
Age 60 and over	70.5%	79.6%	Over 70%	28%
Age 70 and over	77.3%	82.2%	Over 78%	45%

\* The figures in the total column are approximate and were not mentioned by Master et al. They are used here to compare with our total figures since we do not have enough cases to make a separate tabulation of males and females in a statistically significant manner.

in males. However, Bell<sup>8</sup> has written concerning the difficulty in using heart weights as the basis for the diagnosis of hypertension since the weight of the heart varies with the muscular development and weight of the individual. He also stated, "One might expect the weight of the heart to correspond to the intensity of the hypertension, but this is often not the case." As for the actual heart weights, he found that a heart weighing 350 gm. in females and one weighing 400 gm. in males is strongly suggestive of hypertension. Weights of 450 and 500 gm., respectively, nearly always represented hypertensive disease.

Thus, if the lower standards of heart weight are used (300 gm. for females and 350 gm. for males), 35 per cent of the patients in our series had hypertension. If the higher standards are used (350 gm. for females and 400 gm. for males), 25 per cent had hypertension.

In order to compare the weights of the hearts in our series with those in a group of unselected cases, we used 300 autopsy cases from the files of this hospital. These cases were unselected except as to age, all being over 21 years of age (table 2).

A more likely cause of hypotensive tendencies in cirrhotic patients is the generally poor nutritional status of these people. It is thought by some that the beneficial effects of the Kempner<sup>12</sup> rice diet in hypertension is due mainly to a similar effect.

The speculation above, however, is not supported by any factual data at present, so that the lower incidence of hypertension in patients with portal cirrhosis is largely unexplained.

It is realized that definite conclusions of any significance cannot be drawn from this small series. For this reason, it is hoped that the statistics in other hospitals will be evaluated in an effort to clarify this point. Furthermore, if it is found by others that portal cirrhosis and hypertension appear mutually antagonistic, a new approach to the etiology and therapy of the latter may be indicated.

### CONCLUSIONS

The incidence of hypertension in patients with portal cirrhosis is significantly lower than in the general population, using blood pressure readings, heart weights or both, as criteria.

The lower incidence of hypertension in patients with portal cirrhosis is unexplained at the present time.

### BIBLIOGRAPHY

1. CHRISTIAN, H. A., Editor: Oxford medicine, Vol. 5, Part I, p. 374.
2. ROLLESTON, H., and McNEE, J. W.: Diseases of the liver, gall bladder and bile ducts, 1929, Macmillan and Co., Ltd., London, pp. 264 and 573.
3. KIRSHBAUM, J. D., and SHURE, N.: Alcoholic cirrhosis; clinical and pathological study of 356 fatal cases selected from 12,267 necropsies, Jr. Lab. and Clin. Med., 1943, xxviii, 721.
4. BOUCHUT, L., FROMENT, R., and GRASSET: Etat du système cardio-vasculaire dans la cirrhose éthylique du foie, Lyon méd., 1937, clx, 3.
5. MASTER, A. M., MARKS, H. H., and DACK, S.: Hypertension in people over 40, Jr. Am. Med. Assoc., 1943, cxxi, 1251.
6. ROBINSON, S. C., and BRUCER, M.: The range of normal blood pressure, Arch. Int. Med., 1939, lxi, 409.
7. WILBOURNE, M., and CECCOLINI, E. M.: Incidence of hypertension in 25,000 army examinees, Army Med. Bull., 1943, p. 118.
8. BELL, E. T.: Renal diseases, 1946, Lea and Febiger, Philadelphia, pp. 315 and 316.
9. DALEY, R. M., UNGERLEIDER, H. E., and GUBNER, R. S.: Prognosis in hypertension, Jr. Am. Med. Assoc., 1943, cxxi, 383.
10. FISHBERG, A. M.: Hypertension and nephritis, 1930, Lea and Febiger, Philadelphia, p. 141.
11. Criteria Committee of the New York Heart Association: Nomenclature and criteria for diagnosis of diseases of the heart, 4th Edition, 1939, p. 19.
12. KEMPNER, W.: Treatment of kidney disease and hypertensive vascular disease with the rice diet, North Carolina Med. Jr., 1944, v, 125.
13. LICHTMAN, S. S.: Diseases of the liver, 1942, Lea and Febiger, Philadelphia, p. 220.
14. GOODMAN, L., and GILMAN, A.: The pharmacological basis of therapeutics, 1941, The Macmillan Co., New York, p. 795.

entity, or, to express it as would the practicing physician, "When can an actual patient be considered sufficiently examined?" Officially recommended textbooks of medicine<sup>9</sup> omit the subject: without a general introduction, these books begin immediately with chapters in which special topics are discussed. Barker, Christian, and Sir James Mackenzie,<sup>12</sup> in their respective chapters of *Oxford Medicine*, mention it, but not one makes the subject a focal point of discussion. *The Standard Nomenclature of Disease* (*Standard Classified Nomenclature of Disease*)<sup>14</sup> outlines briefly a concept of the disease entity (clinical entity) in its editions of 1933 and 1935, but not in that of 1942. It defines this entity as follows: "Each disease entity is made up of two components: the site and the etiological factor." This characterization of a particular disease has proved its value for cataloguing purposes. However, for a practicing physician or medical research worker, the principle needs to be expanded.

Such a state of affairs in regard to the concept of the clinical entity is unfortunate. It retards the growth of medicine (i.e., of course, clinical medicine—therapeutic or preventive) as a genuine natural science—a most undesirable situation for both patient and physician. Without textbook reference to how medicine arranges its thoughts in general, but with textbook accent solely on "special diseases," the student, particularly the undergraduate one, is easily led to the diagnosis of labels rather than processes, to fit the patient to the cloth rather than the cloth to the patient. He easily falls victim to routine and habit—a temptation difficult to avoid under any circumstances—and may be inclined to consider today's and yesterday's clinical entities as final. He is apt to forget the continuous development of nosography, the fact that at different periods in medical history identical terms express different concepts (e.g., the interstitial nephritis of Bartels and that of Volhard) and different terms similar concepts (e.g., nephrosis and tubular nephritis). He thus loses an insight valuable in deepening his professional understanding that we are in medicine, as elsewhere, not only creators, but also creatures.

Furthermore, this lack of textbook reference produces an intellectual and emotional breach in medical education. Preclinically, the student is taught and trained rigidly to reduce the multiformity of his observations in a given field to a common denominator, e.g., the atom in physics and chemistry, the cell in biology, and the function in physiology. Clinically, he finds an obvious incongruity of denomination; in one instance a topographical designation, such as diseases of the cardiovascular system, in another an etiological one, such as infectious diseases, and in still another a physiological designation, such as diseases of metabolism, etc. The novice at the bedside is thus disillusioned and confused to find so little reference to what seemed to be the core of endeavor in the forefield of his clinical education.

The task of the medical laboratory worker would also be balanced by recognition of the clinical entity. Retired from the natural panorama of events in order to concentrate his attention upon a particular set of signs, the

mass of phenomena encountered in human pathology some significant arrangement of events. The basis for delineation and the actual sets of phenomena that constitute such an arrangement vary at different historical periods.

Physicians, of course, have developed numerous theories concerning the nature of disease, but medical historians tell us that dissenters in theory have often agreed on practical approach to individual patients.<sup>11, 13</sup> It is the clinical entity which bridges the gap between these different theories. Being predominantly a technical tool, it is relatively far removed from the background of theoretical speculation. Cultural differences in the disease concept,<sup>1</sup> however, are not eliminated.

The clinical entity plays different rôles in research and practice: the research clinician is concerned with its development, while the practicing physician is concerned with its application. The former uses single individuals as material to visualize a clinical entity; the latter, on the other hand, uses single clinical entities as material to visualize the individual. The former uses other entities as his standard of comparison, while the latter in final analysis must find his "norm" \* in the patient himself. The creative action of the practicing physician lies in ultimate visualization of the patient as unique and individual (individual diagnosis), despite the necessity of classification as an introductory step.

The general question of individuality leads to consideration of two points of view for biological dynamics—one related to arbitrary repeatable ranges of time (today's experiment will be repeated tomorrow, or, on a larger scale of observation in time, we accept the concept of "eternal laws" in nature),

\* It is important to differentiate the concepts of *mean*, *classical type*, and *norm*.<sup>8, 10</sup> There are two methods of seeing several single variable units as one: *averaging* and *typing*. In the former, single objects under study are measured and the frequency of some is the decisive factor in determining the general unit: the single objects agglomerate around this center in diminishing order. *Mean* is the designation for the kind of general unit obtained by this method. In typing, one views the single objects as non-measurable, individual wholes, and some visualized ideal is the common denominator; the single objects comprehend this ideal in varying degree. *Classical type* is the designation for the kind of general unit obtained by this method.

*Norm* (in biology) is the term used to characterize the actual content of a general unit obtained by either of these two methods. Therefore, depending upon the approach chosen, there are two kinds of biological norm: the *frequency norm* and the *ideal norm*. These may, of course, closely approximate each other.

The characteristics of the method of averaging and of the frequency norm (statistics) are more widely understood than are the principles of the method of typing and of the ideal norm. Since visualization and not frequency plays the decisive rôle in the method of typing, the manifestation of a first and only patient may be sufficient to envision a new classical type, a new clinical entity. Similarly, the ideal norm can refer not only to a group of persons, but to a single one; as outlined in Grote's concept of responsivity, one may visualize the potentiality of a person in comparison to his actuality. Although the classical type and the ideal norm are not derived by calculation, as are the mean and the frequency norm, there is nothing more mystic about them than about any other concept that concerns individuality.

If the subject of reference of the several single units is not variable or if its variability is considered insignificant, no particular term for the general unit is necessary, but the whole group receives a designation, as for instance, *species*, family, etc. In clinical medicine a group of persons exposed to any microorganism or to any drug might be designated as a species. Again, ideal norm and frequency norm may approximate each other.

A discussion of the clinical entity as related to these categories will not be undertaken here.

mal" depend on the patient's age and the irreversibly finite course of life. No other characteristic of the human organism among those mentioned in the biological textbooks needs to be emphasized more to the physician today. Current standard textbooks of physiology do not list the subject of death in their indices, nor is it easy to find a broad and thorough systematic discussion about death from the standpoint of its natural inevitability. However, it is apparent that the phenomenon of physiological death is implied in any concept of at least multicellular life.

Since the days of Hippocrates it has been recognized that the establishment of a normal life-span for all men is too broad for the physician, and the usefulness of subdividing *Homo sapiens* into types of different constitutions, beginning with the obvious sex differentiation, has long been accepted as necessary.

II and III. *The Environmental (Etiologic) and the Topographic Factors.* These two factors help to set the scene for the pathologic-physiologic and the pathologic-morphologic to which the clinical entity and comprehension of the individual patient must ultimately refer.

The *environmental* factor is relatively uncomplicated in analysis. It is simply subdivided into specific and non-specific headings: *conditio sine qua non*, such as infectious and deficiency diseases; and *conditio sine qua etiam*, such as climatic and social factors. Epidemic occurrence, as such, is no longer considered a separate subheading of the environmental factor but rather a combination of a number of factors of the clinical entity.

Literally interpreted, *topographic* factor means a site of involvement. However, it is, of course, not merely the point at which pathologic manifestations appear, but rather the central point of disorder, the prime one from the standpoint of causal relationship (be it mechanical or psychogenic), or a nodal one from the teleologic standpoint. This prime or nodal point may shift during the course of events, resulting in a new entity: for instance, when the pneumonia has been successfully treated, if a secondary empyema remains, the topographic factor of the disease has changed.

Interest and discussion concerning the topographic factor center today around the psychosomatic differentiation and relationship of the organism. It is particularly interesting that a recent investigation<sup>17</sup> suggests a new teleologic perspective regarding the relationship between psychic and somatic disturbances: somatic disease as cure rather than sign of conversion or repression of an unsolved psychic conflict.\*

IV and V. *The Pathologic-Morphologic and the Pathologic-Physiologic Factors.* These factors are closely related, since both structure and function reveal the well or ill being of the organism. Today their close and significant relationship is somewhat underrated in favor of the differences existing between them.

\* The "center" concept versus the "organismic" concept of the structure and function of the central nervous system<sup>7</sup> is a physiologic rather than a topographic problem, but in any event beyond the range of this paper.





its potential (subclinical) form may be discovered by the physician incidentally (e.g., on the occasion of a draft or a life insurance examination). Organic and functional disturbances are often differentiated but both have, of course, a functional disturbance in common. The differentiation lies in the presence or absence of a structural basis for this functional disturbance. (At present the microscopic level of structure is generally taken as a basis—new technics might well alter this baseline.) However, what is the unit of functional disturbance or function in physiology comparable to the cell or the tissue or the organ as units of structure in morphology? The answer to this question reveals a significant cleavage that goes through the present-day human physiological investigation. Extensive specialization by the physiologist has advanced a multiplicity of functional units for consideration, all of value in delineating a clinical entity and in comprehending an individual patient, but with a wide scale of variation regarding the irreversibly finite flow of life. Systems have been fruitfully studied with a minimal amount of such consideration, while organs, tissues and cells, respectively, invite increasing attention to this viewpoint.

It is the aspect of unchanging ("scientific") dynamics that is predominant in studying the pathologic-physiologic factor today, and it seems hardly necessary to point out the extraordinary value of this attitude. The development of this aspect of dynamics has led and will continue to lead to great triumphs in the field of medicine; for as mentioned on page 488, the acceptance of "eternal laws" of nature is the primary basis for intervention and intervention is an ultimate task of the physician; but again—it is only an ultimate one. The physician has first to decide whether or not intervention is indicated. Identical physiologic disorders are not identical clinical entities. Obviously, the hyperthyroidism of acute thyroiditis must be differentiated from that of nodular goiter and the uremia of an acute glomerular nephritis from that of a contracted kidney. Knud Faber devotes the longest chapter of his book to functional diagnosis and says, "Functional diagnosis has directed the footsteps of the clinician who is interested in the methods and data of physiology back to the bedside, where his true kingdom lies . . ." (l.c., page 171). But he also writes, ". . . the functional disturbance is chiefly of interest to the clinician as a means to an end; he is interested in following the course and issue of disease . . ." (l.c., page 164). "Whenever its intimate connection with clinical observation has been broken medical science has been led astray again and again in the days of functional diagnosis as in the days of cellular pathology" (l.c., page 162).




It is not only the natural course, however, which may integrate the five factors mentioned so far, but also the therapeutically-induced one. The success of surgical intervention in restoring normal blood pressures in patients with renal lesions affecting only one kidney brought forth a "new" entity which had been previously entangled in essential hypertension, and for the practitioner, the success of sulfonamide therapy eliminated pneumococcus type differentiation in pneumonia.









*Psychologic Factors:*

	subclinical, incidentally discovered, unknown to both environment and patient
	subclinical to patient, known to environment
	subclinical to environment, known to patient
	overt to both

*Intensity:*

	mild
	moderate
	severe

*Pathodynamic (Pathorrhheic\*)**Factors:*

	early
	intermediate
	late
	progressive
	stationary
	regressive

\* RRHEIC from the Greek RHEO = I FLOW; cf. Dia-RRHEA, Pyo-RRHEA, etc.  
(Or River in the English language.)

(3) *The Clinical Pathological Conference.* There are several aims which a clinical pathological conference can pursue. One, for instance, is to educate the clinician to proper pathological classification on the basis of clinical data. This extolls the clinician who, with a minimum of data and regardless of how the data are collected, is able to provide the proper label of the case in question. It is the correct prediction of this label that counts, and it is immaterial, so far as the conference goes, whether the disease in question is reversible or irreversible, whether a misdiagnosis is made for an acute diffuse glomerular nephritis or for a polycystic kidney. Therapeutic implication is of secondary importance to this type of conference, and outstanding clinicians assert that to excell at the C.P.C. does not necessarily connote excellence at the bedside.

point of view of the natural course of life: internal medicine (including infectious diseases and basic dermatology), psychiatry, pediatrics, and geriatrics. Fortunately, these branches are also still somewhat united from the aspect of their technics. Specialists agree that a competent family physician of such type could be trained in two years. It is true that he would not be able to perform emergency operations beyond highly qualified first aid. It would seem, however, that with such a family physician as basic health consultant all emergencies will be true emergencies and not emergencies arising because of the neglect of people to visit a physician in time. Rare as such true emergencies are, they are best taken care of by specialists and not by someone who may not have performed the required procedure for years even though he had once "learned" it.

Combined rotating internships and assistant residencies established in several medical schools and hospitals seem to indicate a trend in the outlined direction. (See *Training of Physicians for Rural Practice* by William J. Kerr in Second Annual California Rural Health Conference, October 16, 1948.)

It is a great pleasure to acknowledge gratitude to Dr. Owsei Temkin, acting head of the Institute of the History of Medicine of The Johns Hopkins University, for his advice, and to express my appreciation to Mrs. Emily I. Gelperin for her assistance.

#### BIBLIOGRAPHY

Only those publications which are closely related to the subject matter are quoted.

1. ACKERKNECHT, E. H.: Natural diseases and rational treatment in primitive medicine, *Bull. Hist. Med.*, 1946, xix, 467-497.
  2. ALLBUTT, T. C.: A system of medicine by many writers, 1898, Macmillan Company, New York. (1896, MacMillan & Co., Ltd., London.)
  3. CABOT, R. C.: Differential diagnosis, v. 1, 1911, W. B. Saunders Company, Philadelphia and London.
  4. CLENDENING, LOGAN and HASHINGER, E. H.: Methods of diagnosis, 1947, The C. V. Mosby Company, St. Louis, Missouri.
  5. FABER, KNUD: Nosography: The evolution of clinical medicine in modern times, second edition, revised, 1930, Paul B. Hoeber, Inc., New York.
  6. GARBER, S. T.: Stedman's practical medical dictionary, 1942, The Williams & Wilkins Company, Baltimore, Maryland.
  7. GOLDSTEIN, KURT: The organism, a holistic approach to biology derived from pathological data in man, 1939, American Book Company, New York.
  8. GROTE, L. R.: Grundlagen aerztlicher Betrachtung, 1921, Verlag von Julius Springer, Berlin.
  9. Hospital Medical Library Suggestions: *Jr. Am. Med. Assoc.*, 1945, cxxviii, 228-232.
  10. JASPERS, KARL: Allgemeine Psychopathologie, vierte voellig neu bearbeitete Auflage, 1946, Springer Verlag, Berlin and Heidelberg.
  11. NEUBURGER, MAX and PAGEL, JULIUS: Handbuch der Geschichte der Medizin, begrundet von Th. Puschmann, v. 2, 61, 1903, Verlag von Gustav Fischer, Jena.
  12. The Oxford Medicine by various authors, edited by H. A. CHRISTIAN, 1921 (1928), Oxford University Press, New York.
- BARKER, L. F.: The rationale of clinical diagnosis, v. 1, 619-684.  
 CHRISTIAN, H. A.: Present-day medicine, v. 1, 3-11.  
 MACKENZIE, J.: The future of medicine, v. 1, 12-26.

# CASE REPORTS

---

## SALMONELLA ENDOCARDITIS WITH STREPTOMYCIN FAILURE \*

By EDWARD R. H. KURZ, M.D., F.A.C.P., ELMER L. CREHAN, M.D., and  
CHARLES THOMSON, M.D., *White River Junction, Vermont*

MANY reports of endocardial infections, particularly of the subacute variety with response to intensive penicillin therapy, have recently appeared in the literature. Most of these cases are of the *Streptococcus viridans* type. Those associated with other organisms are infrequently reported. This is a report of a case of Salmonella endocarditis without a primary intestinal focus that failed to respond to penicillin, sulfadiazine, or streptomycin, although recognized in its incipency.

The mortality rate in paratyphoid infections is so low that relatively few cases or necropsy reports can be found in the literature. Wells,<sup>6</sup> in reviewing the literature prior to 1904, discovered the mortality rate to be 3.5 per cent for *B. paratyphosus A*, and 4.2 per cent for *B. paratyphosus B*. He noted then that "of 320 necropsies in the paratyphoid infections endocarditis was observed in but one, nor was endocarditis observed in other single necropsies and smaller series, indicating that like typhoid, although a bacteremic disease, paratyphoid does not often lead to an infection of the heart valves."

The largest single series of cases was reported by Rathery and Ambard<sup>4</sup> in 1916. They observed 1,088 cases of paratyphosus B infections which were diagnosed either by positive blood cultures or agglutinations or both. They made no mention of any cases of endocarditis that were diagnosed clinically or observed post mortem.

Kretschmer<sup>2</sup> reported one case of paratyphoid B infection, without the usual intestinal lesions, which showed verrucous vegetations on the aortic cusps with miliary abscesses observed especially in the liver and spleen.

Meyer and Howell<sup>3</sup> reported a case of paratyphosus B infection with vegetations in the aortic and mitral valves which were superimposed on an old endocarditis which may have been rheumatic in nature.

### CASE REPORT

A 59 year old, white, single woodsman was admitted to this hospital for the second time September 12, 1946, with the chief complaint of chills and fever of six days' duration, and shortness of breath of one week's duration. The past history was entirely irrelevant. There was no antecedent history of typhoid or typhoid-like fever. There had been no previous gastrointestinal disturbance, and there was no history of rheumatic fever or rheumatism. The patient was first admitted to this hospital December 2, 1945, with the chief complaint of shortness of breath on exertion. The patient was discharged improved after one month's hospitalization, and the diagnosis

\* Received for publication March 7, 1947.

September 18, the patient's temperature rose to  $102^{\circ}$  and he had an accompanying severe, shaking chill. Chest roentgen-ray and physical examination were essentially the same as on entry. Patient was then given 200,000 units of penicillin daily for six days without relief, so the therapy was discontinued. Patient was uncoöperative and antagonistic and at times appeared to be slightly irrational. He continued to have a daily rise in temperature to  $100^{\circ}$  or  $101^{\circ}$ , and on October 1 streptomycin therapy was instituted. Six grams of streptomycin were given daily for three days without



FIG. 1. December 3, 1945.

response. Because of the lack of therapeutic effect and because of the inaccessibility of the drug, this therapy had to be discontinued. From October 4 to 31, no specific antibiotic therapy was used. The patient's clinical course gradually declined. On October 31, patient again started to have a daily rise in temperature to  $102^{\circ}$  and  $103^{\circ}$ , so sulfadiazine therapy was started. He was given eight grams daily, by the oral method, along with equal doses of sodium bicarbonate. On November 3, patient

because patient still had a daily temperature rise to 103° or 104°. On November 9, streptomycin was obtained and this therapy was again instituted. Patient was given six grams daily. The same day patient complained of right upper quadrant abdominal pain. The liver was four fingers below the right costal margin and tender. There seemed to be some tenderness and spasm in the left upper quadrant but the spleen was still not palpable. On November 10, the patient again had a shower of petechiae in the conjunctivae with a temperature rise to 104.8°. His condition became progressively worse and patient died on November 14, after six days of streptomycin therapy.

#### PATHOLOGICAL DISCUSSION

At post mortem, the body was that of a well-developed and nourished white male, measuring 170 cm. in length and having an estimated weight of 150 pounds. There were petechial hemorrhages in each conjunctiva. There was moderate cyanosis of the nailbeds. No edema was detected.

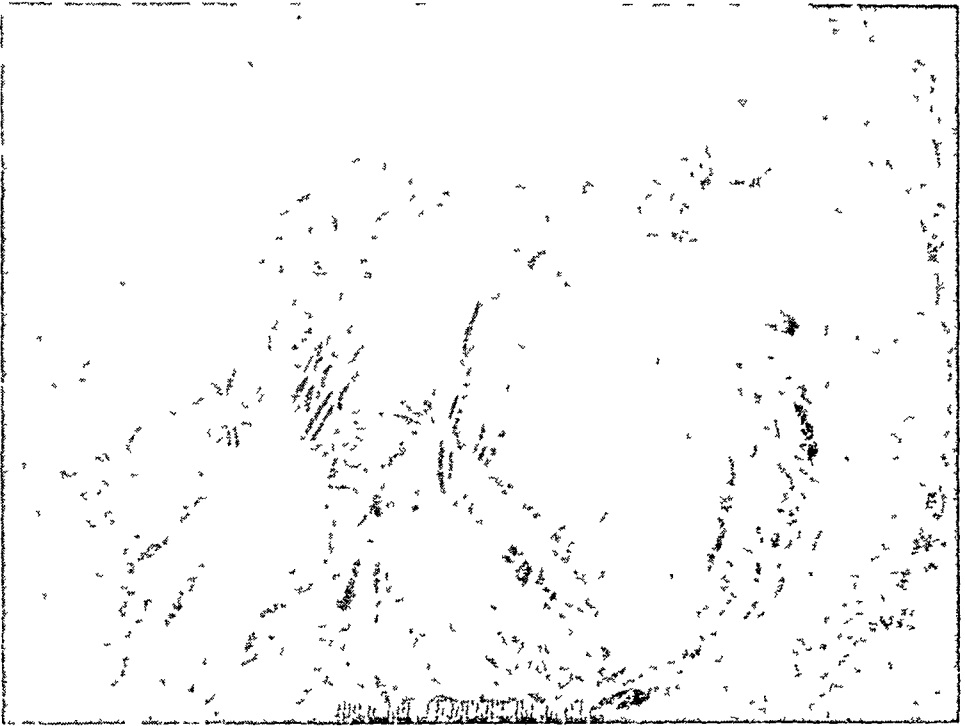


FIG. 3.

Incision revealed a panniculus adiposus of 0.7 cm. with 10 c.c. of clear, yellow, serous fluid in the peritoneal cavity. The greater omentum was plastered to the spleen by firm adhesions. When these were broken an estimated 300 c.c. of purulent liquid was expressed from a splenic abscess. The left pleural cavity contained 200 c.c. of clear, yellow fluid and the right 100 c.c. There were no adhesions.

The pericardial sac contained 100 c.c. of cloudy, yellow fluid. The heart weighed 775 grams. There were prominent, small, dilated vessels and petechiae most prominent over the left auricle. On the left auricular wall, just above the mitral valve, there was a 2 cm. gray, darkened area to which was attached a red, shaggy, friable vegetation. There was some thickening of the mitral valve, but no changes suggestive of old rheumatic valvulitis. The aortic valve was partially replaced by

several dark red, depressed areas as a result of old infarcts. Microscopically both kidneys showed many collections of lymphocytes and a few polymorphonuclear leukocytes in the interstitial tissues of pyramids and the cortices. Many of the tubules contained casts and cellular debris. The remainder of the urogenital system was grossly and microscopically normal.

The central nervous system was normal, both grossly and microscopically.

*Anatomic Diagnoses:* 1. *Salmonella minnesota* endocarditis, aortic and mitral valves, left ventricle and left auricle. 2. Calcareous aortic stenosis. 3. Chronic myocarditis. 4. Abscess of spleen. 5. Chronic pyelonephritis (bilateral). 6. Hypertrophy of the heart (775/375). 7. Focal fibrosis of myocardium. 8. Hydrothorax, 200 c.c. left; 100 c.c. right. 9. Old infarcts of kidneys. 10. Chronic cholecystitis. 11. Cholelithiasis (one stone).

### COMMENT

The etiological organism in this case, recovered by numerous cultures from the blood stream, proved to be *Salmonella minnesota*. At post mortem an intensive search for a primary focus, other than the heart valves, for the source of this organism was made. Gross examination of the gastrointestinal tract revealed no abnormalities. The gall-bladder, other than for a calculus, appeared normal. However, from the gall-bladder proper at post mortem the same organism that was cultured in life was obtained. Whether this was the primary focus or a concomitant infection, we are unable to state.

Discussion as to the underlying pathological cause of the stenosis revealed no history or microscopic changes on the aortic or mitral valves that would lead one to believe that it was due to an underlying rheumatic infection.

This case was treated with all three known antibiotics and, although the diagnosis was made early clinically, the patient's course declined rapidly with ultimate death.

### SUMMARY

Herewith is presented a case of *Salmonella minnesota* infection of the aortic valve, superimposed on an aortic stenosis with bacteremia and septic infection of the spleen, resulting in death despite the use of antibiotics, especially streptomycin.

### BIBLIOGRAPHY

1. CUMSTON, C. G.: Present status of the pathology of the paratyphoids, New York Med. Jr., 1918, cvii, 603.
2. KRETSCHMER, W.: Über die Paratyphus-Sektionsbefunde in Bereich der 1. Armee, Deutsch. Arch. f. klin. Med., 1935, clxxviii, 298-307.
3. MEYER, JACOB, and HOWELL, KATHARINE M.: Acute endocarditis caused by *B. paratyphosus B*, Arch. Path., 1938, xxvi, 368-373.
4. RATHERY, F., and AMBARD, L.: Les fièvres paratyphoides B à l'hôpital mixte de Zuydcoote de decembre 1914 a fevrier 1916, Paris, Felix Alcan, 1916.
5. VOGELSANG, T. M.: Paratyphoid B in Western Norway; bacteriology, symptomatology, morbid anatomy and epidemiology of infection associated with *B. paratyphosus B*, Jr. Infect. Dis., 1934, Iv, 276-298.
6. WELLS, H. G.: Acute endocarditis produced by *Bacillus paratyphosus*, Arch. Path., 1937, xxiii, 270-274.

During the initial examination November 8, 1946, the patient was acutely restless although in no obvious respiratory embarrassment, somewhat pale with beads of perspiration on the upper lip and covering the brow. General examination was negative with the exception of a pulse rate approximately 180 per minute. The first electrocardiogram, made about seven hours after the episode began (figure 1), showed paroxysmal tachycardia with a QRS interval of 0.14 second, and a ventricular rate absolutely constant at 188 per minute. Following the examination, the patient in-

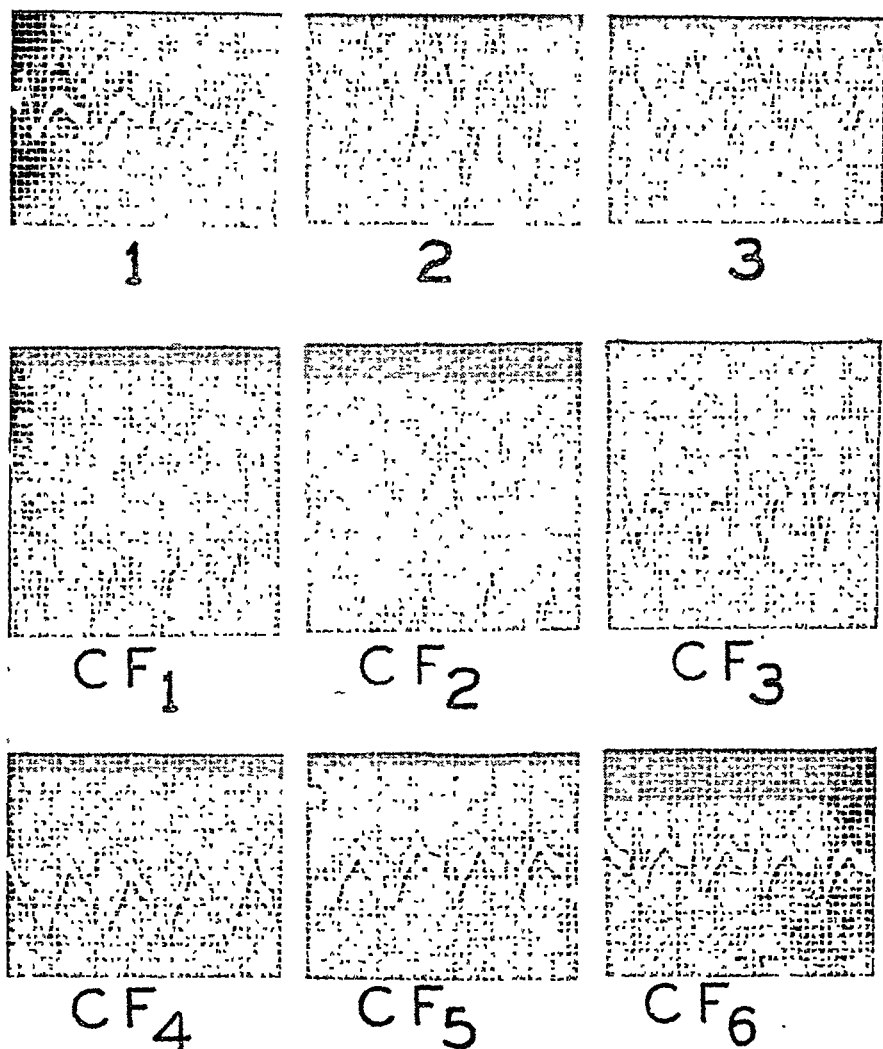


FIG. 1. C.V.B., November 8, 1946. Electrocardiogram made seven hours after onset of the tachycardia, presumably ventricular in origin.

sisted upon driving his car home, a distance of some 17 miles, where he continued under the observation of his referring physician, who, on the following afternoon, gave the patient 3 grains of quinidine sulfate every four to six hours by mouth. After the second dose the attack subsided, having lasted a total of 26 hours.

Three days following the onset of this episode (or two days after its subsidence) the patient returned for his second electrocardiogram. At this time he had been at least 40 hours without medication, had completely recovered his composure and sense

version of the T waves in Leads II and III with a widening of the Q-T interval to 0.48 second. Deep S waves were persistent throughout all limb leads and there was a late T<sub>1</sub> inversion. The chest leads showed conspicuously tall T waves in CF<sub>1, 2 and 3</sub> with late inversion of the T waves in CF<sub>4, 5 and 6</sub>. A physical examination at this time was again completely negative, blood pressure 120/80, white blood count 14,200; polymorphonuclears 72 per cent; red blood count 4.52; hemoglobin 88 per cent, blood Mazzini test negative, and sedimentation rate normal. Chest fluoroscopy was normal, the heart and great vessel shadows being well within normal limits. Subsequent electrocardiograms (figure 2) made nine days (November 18, 1946) and 23 days (December 2, 1946) after subsidence of the attack showed persistency of the P-R interval at 0.22 second and QRS interval at 0.09 second, lessening of the T wave inversion in the limb leads, changing to upright T waves in all limb leads on the twenty-third day following cessation of the attack. The RS-T segment alterations had disappeared by the ninth day. Physical examinations on each of the days in which electrocardiograms were done were negative, and sedimentation rates in each instance were normal.

### DISCUSSION

Close analysis of the initial cardiogram (figure 1, November 8, 1946) made at the seventh hour of the episode of rapid heart action showed QRS-T complexes of the same character within each lead, suggesting unifocal origin of the ectopic beats. The actual effect of the rapid heart action on the sinus node cannot be determined in this instance since it is impossible to make out the P waves during the paroxysm, and no record is available of the onset of the episode; in the absence of recognizable P waves, it is possible but improbable that this may represent an instance of supraventricular paroxysmal tachycardia with intraventricular block, but this is unlikely because the intraventricular block had disappeared in the first tracing following cessation of the ectopic rhythm, suggesting that the intraventricular block was related to the rapid heart beating rather than a pre-existent bundle branch block; furthermore, there is no similarity of contour of the QRS configuration in the tracing made during and after the abnormal rhythm. Katz<sup>8</sup> has recently published records demonstrating the value of the QRS pattern occurring between attacks of paroxysmal tachycardia in distinguishing between one of a supraventricular origin associated with intraventricular block, and one of pure ventricular origin. Supporting the belief that this tachycardia was ventricular in origin is the fact that carotid sinus massage had no effect on the rate or rhythm.

The ECG abnormalities of the cardiogram (figure 2, November 11, 1946) made two days after cessation of the 24 hour attack of rapid heart action showed depression of RS-T<sub>2 and 3</sub> with plus-minus diphasicity of T<sub>1</sub>, a striking inversion of T<sub>2 and 3</sub> having broad bases with equal limbs, and prolongation of Q-T interval (actual 0.48 second, as compared to predicted upper limit of normal at 0.40 second, using the Ashman-Hull<sup>9</sup> formulae). In addition, important changes occurred in the chest leads: there was elevation of RS-T segments in CF<sub>1, 2 and 3</sub> with conspicuously tall and upright T waves, having very broad bases and almost equal limbs; in CF<sub>4</sub> there was definite late inversion of the T wave—resembling somewhat that of Lead I—and late T wave inversion in the CF<sub>5 and 6</sub> positions. The subsequent cardiograms showed a gradual restoration to normal, with recovery of the RS-T segment deviation in limb and chest leads by the ninth day after cessation of the attack (figure 2, November 18, 1946), and recovery of T



(March 29, 1947) in order to demonstrate its stability at normal values. In all the electrocardiograms following the initial episode of tachycardia, there is a P-R interval varying from 0.22 to 0.24 second in accordance with the heart rate and representing what is apparently "normal" for this heart. Recent studies of

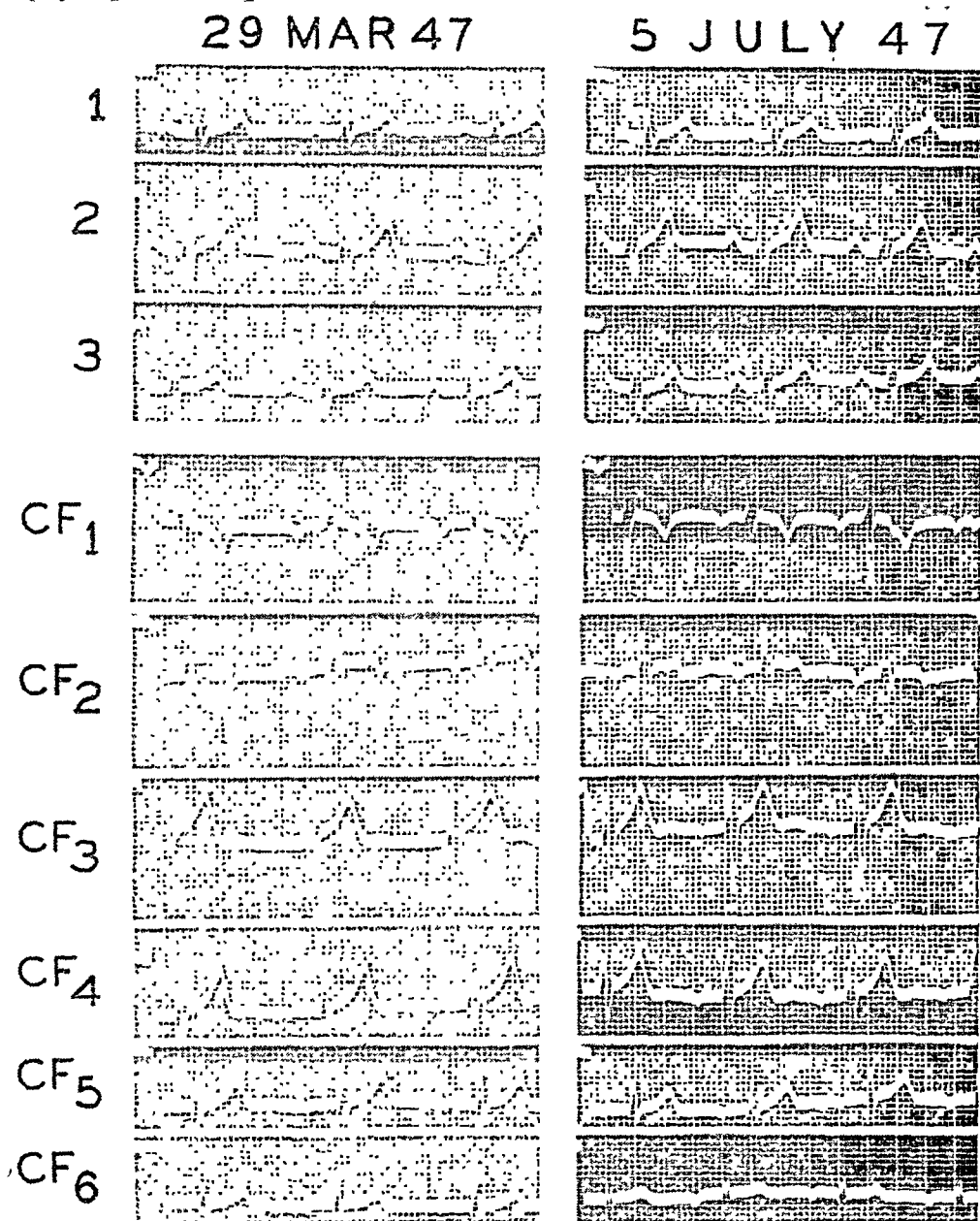


FIG. 4. The electrocardiogram dated March 29, 1947 was made 123 days after offset of the tachycardia; the tracing dated July 5, 1947 shows stabilization of the two records at normal values except for prolongation of P-R intervals.

Graybiel et al.<sup>10</sup> reported P-R intervals of 0.22 second or greater in 12 out of 1000 healthy aviators; Hall, Stewart, and Manning<sup>11</sup> found P-R intervals greater than 0.20 second in nearly 2 per cent of 2000 RCAF aircrew.

8. KATZ, L. N.: *Electrocardiography*, 1946, Second Edition, Lea & Febiger, Philadelphia, p. 634.
9. ASHMAN, R., and HULL, E.: *Essentials of electrocardiography*, 1937, First Edition, Macmillan Co., New York, p. 93 and 205.
10. GRAYBIEL, A., MCFARLAND, R. A., GATES, D. C., and WEBSTER, F. A.: Analysis of the electrocardiograms obtained from 1000 young healthy aviators, *Am. Heart Jr.*, 1944, xxvii, 524.
11. HALL, G. E., STEWART, C. B., and MANNING, G. W.: The electrocardiographic records of 2,000 RCAF aircrew, *Canad. Med. Assoc. Jr.*, 1942, xlii, 226.
12. COSSIO, P., VEDOYA, R., and BERCONSKY, I.: Modifications of the electrocardiogram following certain attacks of paroxysmal tachycardia, *Rev. argent. de cardiol.*, 1944, xi, 164.
13. LEWIS, T., ORURY, A. N., WEDD, A. M., and ILIESCU, C. C.: Observations upon the action of certain drugs upon fibrillation of the auricles, *Heart*, 1922, ix, 207.
14. DELEVETT, A. F., and POINDEXTER, C. A.: Plasma concentrations of quinidine with particular reference to therapeutically effective levels in two cases of paroxysmal nodal tachycardia, *Am. Heart Jr.*, 1946, xxxii, 697.

---

## STREPTOMYCIN THERAPY OF *HEMOPHILUS INFLUENZAE* ENDOCARDITIS LENTA \*

By WILLIAM S. MIDDLETON, M.D., F.A.C.P., *Madison, Wisconsin*

RENEWED interest in the etiology of endocarditis lenta has been a natural by-product of the availability of a series of agents with therapeutic promise. The success attendant upon the use of penicillin in treating *Streptococcus viridans* endocarditis lenta gave further impetus to similar attacks upon other etiologic backgrounds. Among these, *Hemophilus influenzae* and *para-influenzae* invited particular attention by reason of their sensitivity to streptomycin.

The incidence of *Hemophilus influenzae* and *para-influenzae* endocarditis is probably less common than Thayer's 2.94 per cent.<sup>1</sup> In 1940 Craven, Poston and Orgain<sup>2</sup> collected only 36 instances of this condition from the literature, to which they added two patients. Rose,<sup>3</sup> Hunter and Duane<sup>4</sup> and Martin and Spink<sup>5</sup> likewise emphasized its rarity. By reason of this circumstance and the remarkable clinical response to streptomycin this case record is posted:

A 37 year old white farmer was admitted to the Wisconsin General Hospital, September 30, 1946, complaining of chills and fever.

In the spring of 1945 the patient had noticed the gradual onset of malaise and easy fatigue. In about six weeks chills made their appearance. The first chill lasted about one-half hour and was succeeded by fever of 103° Fahrenheit for three hours. The interval between the chills decreased until they were occurring about a week apart. On two occasions there were two chills at two hour intervals in the same day. The chills lasted from 20 to 35 minutes and the fever, usually for about three hours. The sweating was profuse. Frequently after the fever there were observed local areas of discoloration 2.5 to 3 cm. in diameter with spontaneous aching and marked tenderness. These remained painful for about a week to 10 days.

The patient came under the care of several physicians beginning July 22, 1945.

\* Received for publication December 2, 1947.

From the Department of Medicine, University of Wisconsin Medical School.

Duane<sup>4</sup> and Bland and Peterson<sup>7</sup> have reported isolated instances of the clinical cure of *Hemophilus influenzae* or *para-influenzae* endocarditis lenta by streptomycin. (The latter authors indicate a second arrest of this infection under streptomycin.) Although this condition may be unusual, its earlier diagnosis in the patient herein discussed was twice overlooked by competent clinical pathologists and clinicians through the neglect of positive returns upon blood culture. Possibly this etiology of endocarditis lenta may not be as rare as is generally assumed.

#### BIBLIOGRAPHY

1. THAYER, W. S.: Bacterial or infective endocarditis, *Edinburgh Med. Jr.*, 1931, xxxviii, 237 and 307.
2. CRAVEN, E. B., JR., POSTON, M. A., and ORGAIN, E. S.: *Hemophilus parainfluenzae* endocarditis, *Am. Heart Jr.*, 1940, xix, 434.
3. ROSE, H. M.: *Hemophilus influenzae* Type A endocarditis, *Am. Jr. Med. Sci.*, 1941, ccii, 187.
4. HUNTER, T. H., and DUANE, R. B., JR.: Subacute bacterial endocarditis due to gram negative organisms, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 209.
5. MARTIN, W. B., and SPINK, W. W.: Endocarditis due to Type B *Hemophilus influenzae* involving only the tricuspid valve, *Am. Jr. Med. Sci.*, 1947, ccxiv, 139.
6. PRIEST, W. S., and MCGEE, C. J.: Streptomycin in the treatment of subacute bacterial endocarditis, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 124.
7. BLAND, E. F., and PETERSON, E. W.: Cases from Medical Grand Rounds, Massachusetts General Hospital, Case 14, Subacute bacterial endocarditis, *Am. Practitioner*, 1947, i, 498.

---

### VENA CAVAL THROMBOSIS WITH POLYCYTHEMIA AND LEG ULCER\*

By JOHN A. BOONE, M.D., F.A.C.P., and HORACE G. SMITHY, M.D.,†  
Charleston, South Carolina

THE first case of vena caval thrombosis associated with polycythemia was reported by Ragins and Coe in 1943.<sup>1</sup> In their patient the polycythemia developed under observation subsequent to a thrombosis of both the superior and inferior vena cava. The patient did not recover and an autopsy disclosed the vena caval obstruction which had been suspected clinically. Before the thrombosis the hemoglobin was 85 per cent and the red blood count 4,900,000. After the thrombosis the hemoglobin rose to 100 per cent and the red blood count to 7,960,000.

We wish to report a similar case which recovered and subsequently developed varicose ulcers of the legs.

#### CASE REPORT

The patient, a white female aged 61 years, entered Roper Hospital on February 2, 1946, complaining of pain in the legs. Two years previously she had awakened one morning "swollen all over," and the joints of her entire body became stiff. Her local

\* Received for publication April 16, 1947.

From the Departments of Medicine and Surgery, Medical College of South Carolina and Roper Hospital, Charleston, S. C.

† Deceased.

showed pronounced dependent cyanosis and rubor and numerous small superficial varices. In the right leg there was a questionably positive Homans' sign, deep calf tenderness and acute tenderness in the femoral triangle. There was no edema, but the patient had been in bed several weeks. Both posterior tibial pulses were palpable; both anterior tibial pulses were absent. There was a healed ulceration on the lower third of the right leg with surrounding pigmentation.

Laboratory studies showed the urine within normal limits. The red blood count was 7,650,000, the hemoglobin 18 grams per 100 c.c., the white blood count 13,700 with 81 per cent polymorphonuclears.

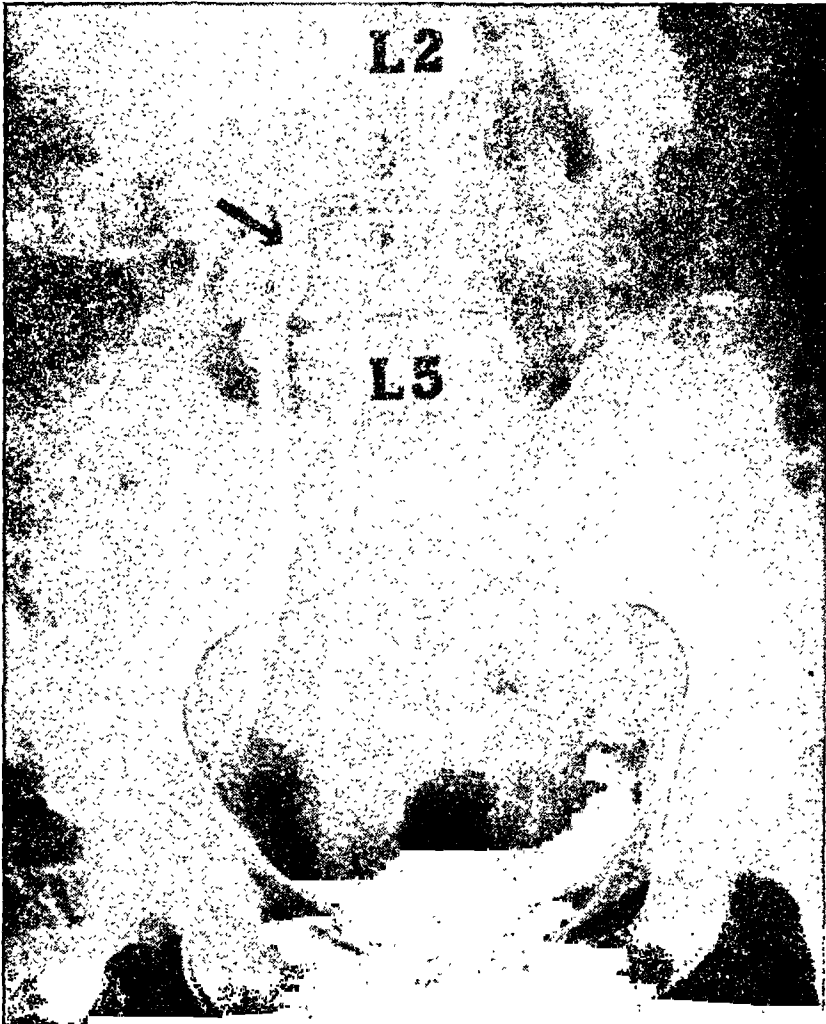


FIG. 2.

It was thought that the patient had an acute recurrent thrombophlebitis in the right leg. A novocaine block of the right lumbar sympathetic chain resulted in complete elimination of pain, Homans' sign and palpatory tenderness. Her general condition was not considered sufficiently good to permit the performance of lumbar sympathectomy. Accordingly, an alcohol injection of the right lumbar sympathetic chain was done and the patient was discharged. She remained free of pain for several months. In June, 1946, she developed upper abdominal pain, nausea and vomit-

## BIBLIOGRAPHY

1. RAGINS, O. B., and COE, G. C.: Superior and inferior venae cavae thrombosis with polycythemia; report of a case, *Ann. Int. Med.*, 1943, xix, 496-501.
  2. SMITHY, H. G.: Complicating factors in the surgical management of varicose veins with special reference to interruption of sympathetic nerve impulses as an adjunct in treatment, *Surgery*, 1945, xvii, 590.
- 

## PERSISTENT TACHYCARDIA CAUSED BY SNAKE VENOM \*

By W. H. GLASS, M.D., *Hartford, Connecticut*

THE venom of the water moccasin snake (*Ancistrodon piscivorus*) is used with some frequency in a heterogeneous group of diseases manifesting excess bleeding. Pecke and Rosenthal<sup>1</sup> reported enthusiastically about its beneficial effects in epistaxis of long standing, excess uterine bleeding, Osler's disease (hereditary hemorrhagic multiple telangiectasis), and various forms of purpura based on either toxic, allergic, or endocrinal abnormality. They state categorically that there are no contraindications to snake venom therapy. The venom was given subcutaneously for systemic effects in their series of cases, as has become the accepted procedure.

The venom of the Fer-de-lance (*Bothrops atrox*) is packaged and used for local hemostasis in instances where bleeding surfaces are readily available and where excessive bleeding can be anticipated, as following dental extraction or tonsillectomy. It is felt that snake venoms, in general, precipitate the clotting mechanism and do not require the action of thrombokinase, calcium, or prothrombin for the coagulation of fibrinogen to fibrin.

The venom of the cobra is used clinically as an analgesic. Macht<sup>2</sup> summarizes the work done in this field using cobra venom as a post-operative analgesic and in pain-producing malignancies. He has had no instances of toxicity, except slight to moderate discomfort at the site of the injection, and feels that its efficacy is greater than the opiates or the newly developed synthetic narcotics. In no instance has he had to discontinue the use of the drug because of untoward reactions.

Physiological research in reptile and insect venom has shown adverse effects following large dosages . . . comparable to the dose injected by the animal in the act of defending itself or in the act of food-seeking. Essex<sup>3</sup> gives a detailed review of the effects on circulation and the variable degrees of heart block in various experimental animals. In no instance was tachycardia produced. Brown,<sup>4</sup> in investigating the effects of water moccasin venom in large doses on dogs, shows that "there is a definite relationship between the quantity of venom injected and the cause of death: the heavier doses yield the neurotoxic (central) effects and the lighter doses yield the 'shock' (peripheral or circulatory) effects." Further work<sup>5</sup> by the same investigator shows that strong venom solutions slow the heart initially by action on the vagus mechanism, probably the ganglion cells. This effect can be abolished by atropin. The latter conclusions were arrived at following work on the isolated amphibious heart.

\* Received for publication April 11, 1947.

urine examinations were essentially normal. Her basal rate was plus 41 per cent. General examination was negative, except for a thyroidectomy scar. No underlying thyroid tissue could be palpated. Physical examination and fluoroscopy of the heart showed only a tachycardia. Electrocardiogram showed a regular sinus rhythm with a rate of 140. There was slurring of the QRS complex in limb Lead I, and in precordial leads CF<sub>2</sub> and CF<sub>4</sub>. There were no essential variations in either intervals, rate or tracing contour in various positions, or during unilateral or bilateral carotid sinus massage. The initial impression here was a supra-ventricular tachycardia of undetermined etiology. The patient was placed on quinidine sulfate grains 3 four times a day. Following eight days of this medication there was a slight decrease in pulse rate, but within one more week she had returned to the original status, and had begun to present signs of heart failure manifested by dyspnea at rest and transient ankle edema. At this time she was placed on thiouracil, 0.2 gm. three times a day. This had to be decreased because of nausea, and then continued in lesser amounts. Following three weeks of this therapy there was no significant variation and the thiouracil was discontinued.

At this time, the patient was re-hospitalized for further study. She presented a moderate secondary anemia, early manifestations of multiple vitamin deficiencies, a basal metabolic rate of plus 31, and a blood cholesterol of 175 mg. per cent. Snake venom was discontinued. Large amounts of enteral and parenteral vitamin preparations were given, and the patient was urged to increase her grossly deficient food intake. Within two weeks she began to have increased nasal bleeding and had to be fulgerated topically. Shortly after this, 21 days after the discontinuance of snake venom, she developed a full-blown picture of myxedema with a normal heart rate, gross obesity and a classical distribution of cutaneous edema. Her basal metabolic rate decreased to minus 32. She was placed on desiccated thyroid tissue orally, which had to be increased to 20 to 25 grains per day to bring her to a normal metabolic status. Now with periodic nasal mucous membrane fulgeration, and intensive anti-allergic measures, she has occasional minor bleeding episodes, but is otherwise asymptomatic.

### SUMMARY

An instance of familial hereditary hemorrhagic telangiectasis is presented that was treated with snake venom for massive epistaxes. She responded satisfactorily, with a diminution in her nasal bleeding. She developed, however, a syndrome simulating hyperthyroidism sufficiently closely to warrant thyroidectomy. This operation did not halt the progress of the disease. With the discontinuance of snake venom the entire picture changed to post-operative myxedema. Her nasal bleeding has been kept under control by fulgeration. This is the first instance of this type of response recorded. One is unable to tell whether allergy is a responsible factor or whether this is a drug idiosyncrasy.

### BIBLIOGRAPHY

1. PECKE, S. M., and ROSENTHAL, N.: Effect of moccasin snake venom (*Ancistrodon piscivorus*) in hemorrhagic conditions, Jr. Am. Med. Assoc., 1935, civ, 13.
2. MACHT, D. I.: Recent development in pharmacology of cobra venom, Med. Rec., 1941, cliii, 369-375.
3. ESSEX, H. E.: Certain animal venoms and their physiologic action, Physiol. Rev., 1945, xxv, 148-170.
4. BROWN, R. V.: The effects of water moccasin venom on dogs, Am. Jr. Physiol., 1941, cxxxiv, 202-207.
5. BROWN, R. V.: The action of water moccasin venom on the isolated frog heart, Am. Jr. Physiol., 1945, cxxxviii, 613-619.

## CASE REPORTS

*Case 1.* The first patient to be treated with stilbamidine was a 23 year old Negro, who was admitted to the Michigan Rapid Treatment Center on March 6, 1945. This man had developed a small penile sore in February of 1942. The blood serology at that time was negative, and remained so when repeated in August 1942, January 1943, and March 1943. Despite this fact and the chronicity of the lesion, a physician made a presumptive diagnosis of primary syphilis and administered four injections of neoarsphenamine. Despite some improvement in the appearance of the ulcer, the patient discontinued treatment. No further therapy was received until after his admission to the Rapid Treatment Center.

During the interval of two years between the administration of neoarsphenamine and his admission to the Center the lesion had increased in size very slowly, and on occasion was moderately painful. The sole constitutional manifestation of illness was a 10 pound weight loss.

On admission to the Rapid Treatment Center, the penis presented a secondarily infected ulceration of the glans and prepuce. Induration was slight, and tenderness minimal. Bilateral inguinal lymphadenopathy was present, the nodes being slightly enlarged, discrete, and rubbery to palpation. Neither the liver nor spleen was palpable. A chest roentgenogram appeared normal.

Thorough laboratory study revealed no evidence of syphilis, chancroid, lymphopathia venereum, or granuloma inguinale. Urinalysis was normal. The hematological examination was normal except for a slight leukopenia, 4,900 cells per cu. mm., and a differential count showing 44 per cent neutrophilic granulocytes, 37 per cent lymphocytes, 16 per cent monocytes, and 3 per cent eosinophiles. The total serum proteins were 8.7 gm. per cent with an A-G ratio of 1. Biopsies taken from the penile ulcer and the inguinal lymph nodes were diagnosed as histoplasmosis. Blood agar cultures made from this material yielded a growth of *Histoplasma capsulatum*. The histoplasmin skin test was negative.

Because of his excellent general condition, and the presence of a local lesion whose progress could be followed with ease, it was decided to treat him with stilbamidine. Local application of penicillin was used for a short time to aid in overcoming the secondary infection. Potassium permanganate soaks, 1:8,000, were occasionally used for the same purpose. Stilbamidine was administered intravenously in the amount of 2.5 to 3.0 mg. per kg. of body weight per injection. The drug was prepared in distilled water.

From April 12, 1945 until May 9, 1945, he received a total of 3,534 mg. of the drug. He was then discharged for a rest period, and was readmitted on June 13 of the same year. From this latter date until August 14, 1945, he was given a total of 3,923 mg. of stilbamidine. The administration of the second course was delayed and hampered by severe urticarial reactions which appeared to be allergic in nature. However, when the method of preparing the solution was changed, and it was stored only for a day or two in a brown glass bottle, no further difficulty was experienced.

At the time of discharge, the lesion had improved in appearance. Local edema had decreased, and some degree of epithelialization was present. However, he had experienced moderate anorexia, occasional headache, and slight weight loss. The total white blood cell count was now 3,950 per cu. mm. His general physical appearance was not as good as on his first admission. Just prior to discharge from the hospital, the penile lesion was again biopsied. *Histoplasma capsulatum* were found in abundance. There was neither pathological nor clinical evidence that stilbamidine had exerted a significant therapeutic effect. He was afebrile throughout both hospital admissions. The total dose of stilbamidine which he received was 7,457 mg.

*Case 2.* The second case to be given stilbamidine was a 61 year old white male, who was first seen in the Otology Clinic of the University Hospital on April 3, 1945,

ber 27, 1945. His neck was swollen and presented a firm, hot, red, pulsating mass anterior to the sternocleidomastoid muscle and just superior to the right clavicle. The mass was fluctuant. Massive edema of the epiglottis and aryepiglottic folds was present. His temperature fluctuated between 101° F. and 103° F., for three days prior to incision and drainage of the neck abscess. Following drainage, he was afebrile for one week but then showed frequent elevations of his temperature, not exceeding 100° F. The total white blood cell count was normal, but the differential revealed 13 per cent monocytes. During this admission he suffered one moderate hemorrhage from the nose and mouth. Paresthesias in the trigeminal distribution were present bilaterally, both corneal reflexes were absent, a corneal ulcer was present O.D. A tarsorrhaphy was performed on the right. A chest roentgenogram taken during this admission showed no active pulmonary disease. He was discharged to the Wayne County Infirmary for terminal care on February 8, 1946.

From February 8, 1946 until his death on April 11, 1946, his course was simply one of progressive respiratory distress and recurrent bleeding from the tracheotomy tube. His temperature fluctuated between 99° and 101° F. No autopsy was obtained. He had received a total of 6,275 mg. of stilbamidine.

### SUMMARY

A report is given of the response of two patients with histoplasmosis when treated with stilbamidine. Insufficient data are available to evaluate the adequacy of the total dose given to these patients. Factors of drug fastness or increasing resistance are not known, and it may be that an interrupted series of injections was chosen unwisely. However, both patients received a total dose at least equal to the average reported for the treatment of kala-azar and trypanosomiasis, and the method of administration has been used widely. One patient exhibited a toxic manifestation of the drug, cranial nerve palsy (trigeminal).

Both of the patients in this report showed several features of histoplasmosis which do not seem to be known generally. Histoplasmosis is not infrequently a localized granuloma which remains such for relatively long periods of time. When the disease is recognized before the patient is aware of constitutional manifestations of disease, there is often no fever, hepatomegaly, splenomegaly, anemia, or leukopenia. Neither of these patients reacted to skin-test doses of mycelial histoplasmin and neither had infections of a type which might induce a state of anergy. The histoplasmin used was known to be active. One of the patients did react to a heat-killed vaccine made from the yeast form of the organism.

Although both patients were regarded initially as demonstrating improvement while under treatment with stilbamidine, this was temporary and the drug could not be said to have modified the course of the disease to a significant degree.

### BIBLIOGRAPHY

1. PARSONS, R. J., and ZARAFONETIS, C. J. D.: Histoplasmosis in man: Reports of seven cases and a review of 71 cases, Arch. Int. Med., 1945, lxxv, 1-23.
2. SEABURY, J. H., and ARTIS, D.: In vitro susceptibility of *Histoplasma capsulatum* to therapeutic agents, Proc. Soc. Exper. Biol. and Med., 1946, lxi, 15-16.



mechanism might be at work in man. Ryland<sup>5</sup> in 1933 demonstrated that digitalis lowered venous pressure in normal man, and Wood<sup>6</sup> in 1940 showed that the drug reduced venous pressure in patients with heart failure, independently of any change in heart rate. He also adduced evidence against the hepatic vein "throttle" mechanism suggested by Dock and Tainter a decade earlier.

Forssmann's technic of intracardiac catheterization,<sup>7</sup> developed by Cournand and Ranges in 1941,<sup>8</sup> has afforded a new, easy and accurate method of obtaining serial readings of right auricular pressure and cardiac output. This method gives fair promise to settle the long disputed mechanism of digitalis action in congestive failure. McMichael and his colleagues, at the Postgraduate School in London, have been the first to take advantage of this technic, and the results of their early investigations were published in 1944.<sup>9</sup> They first made 25 series of observations on a group of 24 patients; three of these had normal hearts, while the remainder suffered from some form and degree of heart failure. The diseased group included patients with hypertensive, valvular and coronary disease, and others with anemia, cor pulmonale and thyrotoxicosis. The one constantly observed effect of 1.5 mg. digoxin administered through the catheter was a fall of right auricular pressure. This occurred in each and every patient, in the normals and in those with cardiac failure alike. Cardiac output, on the other hand, behaved variously: it rose in 15, it fell in seven, and in three there was no significant alteration. Scrutiny of these results showed that there was a nice correlation between the initial level of output, and its response to digoxin. Thus, those patients whose output had been normal or high before digoxin was administered, showed a fall in output after digitalization; this group was composed of the normal patients and those with cor pulmonale and anemia. On the other hand, those who had a low initial output responded to digoxin with a rise in output; this larger group contained the hypertensive, valvular, coronary and thyrotoxic failures. Twelve further cases with a low initial output have subsequently been studied and reported.<sup>10</sup> In all of these also, the right auricular pressure fell while the output rose significantly after digoxin.

From this analysis the authors introduce the concept of "High Output" and "Low Output" failure. They propose that high output failure is caused by conditions which demand an increase in the output of the heart, such as

<sup>5</sup> RYLAND, D. A.: The effect of digitalis on the venous pressure of normal individuals, *Jr. Clin. Invest.*, 1933, xii, 847.

<sup>6</sup> WOOD, P.: The action of digitalis in heart failure with normal rhythm, *Brit. Heart Jr.*, 1940, ii, 132.

<sup>7</sup> FORSSMANN, W.: Die Sondierung des rechten Herzens, *Klin. Wchnschr.*, 1929, viii, 2085.

<sup>8</sup> COURNAND, A., and RANGES, H. A.: Catheterization of the right auricle in man, *Proc. Exper. Biol. and Med.*, 1941, xlii, 462.

<sup>9</sup> McMICHAEAL, J., and SHARPEY-SCHAFER, E. P.: The action of intravenous digoxin in man, *Quart. Jr. Med.*, 1944, xiii, 123.

<sup>10</sup> HOWARTH, S., McMICHAEAL, J., and SHARPEY-SCHAFER, E. P.: Effects of venesection in low output heart failure, *Clin. Sci.*, 1946, vi, 41.

It could be argued that in low output failure, the fall in right auricular pressure which follows digitalization is the result and not the cause of the improved output—the output rising as a result of the stimulating action of digitalis on the ventricular muscle. The authors, therefore, investigated the effect of congesting cuffs to the thighs and venesection,<sup>10</sup> both of which measures must operate primarily by reducing venous filling pressure. They found that in four patients subjected to congesting cuffs, and in 10 subjected to venesection, the same augmentation of cardiac output occurred as was observed to accompany a similar reduction of right auricular pressure by digitalis. This finding shows that simple reduction of venous pressure is enough to increase output, and therefore makes it at least unnecessary to hypothesize that the reduction in venous pressure is the result of increased output. Against the belief that digitalis acts as a stimulant of heart muscle, McMichael quotes the work of Katz and his associates<sup>11</sup> who showed that digitalis had no effect on the contractility of isolated dog myocardium.

In this connection it is interesting to notice that many pharmacological experiments on the effects of glycosides on cardiac output have been made with strophanthin. Results obtained with this drug have sometimes been assumed to hold true for digitalis. It is therefore intriguing to find that McMichael claims,<sup>12</sup> as a result of his clinical experiments, a decided difference in the effects of the two glycosides, digoxin and g-strophanthin, on venous pressure and cardiac output. The difference is beautifully illustrated in emphysema hearts. In these cases (high output failure) digoxin reduced the right auricular pressure and with it, in most cases, the cardiac output was lowered<sup>13</sup>; whereas strophanthin often increased the output without having any appreciable influence on the right auricular pressure. He concludes that, while the primary and principal action of digoxin is to reduce venous pressure, that of strophanthin is to stimulate the myocardium. This may prove to be a point of clinical value, for, while digitalis may be ineffective in cor pulmonale,<sup>14</sup> and even actually harmful, strophanthin may be of definite benefit.

There are other interesting facets to McMichael's work. He has confirmed the point made by Wood<sup>6</sup> that slowing of the heart by digitalis is an insignificant factor in the control of congestive failure. Wood showed that the venous pressure continued to fall in response to digitalis, even if the heart rate increased as a result of some coincident stimulus (a full bladder, atropine). McMichael has gone further and demonstrated that in failure, with either sinus rhythm or auricular fibrillation, the venous pressure falls and the cardiac output increases after digitalis, even if the heart rate increases

<sup>11</sup> KATZ, L. N., MENDLOWITZ, M., and KAPLAN, H. A.: Action of digitalis on isolated heart, *Am. Heart Jr.*, 1938, xvi, 149.

<sup>12</sup> McMICHAEAL, J.: The pharmacology of the failing heart, *Brit. Med. Jr.*, 1948, ii, 927.

<sup>13</sup> HOWARTH, S., McMICHAEAL, J., and SHARPEY-SCHAFER, E. P.: Effects of oxygen, venesection and digitalis in chronic heart failure from disease of the lungs, *Clin. Sci.*, 1947, vi, 187.

<sup>14</sup> VAQUEZ, H., and LUTEMBACHER, R.: De l'Ouabaine Arnaud, *Presse méd.*, 1928, xxxvi, 129.

## REVIEWS

*Regional Ileitis.* By BURRILL B. CROHN, M.D., Consulting Gastroenterologist, Mt. Sinai Hospital, New York. 229 pages, 14.5 × 22 cm. Grune and Stratton, Inc., New York, N. Y. 1949. Price, \$5.50.

It is a pleasure to review this volume for it not only represents the first book on the subject of "Regional Ileitis" but it comes from the rich experience of a pioneer observer of the disease. Although the condition has oftentimes been referred to as "Crohn's" disease, the author, in all modesty, uses only the designation "regional ileitis." The book represents 18 years of careful study and analysis of 298 cases of regional ileitis in all its forms. No wonder, then, that a clear cut clinical picture evolves even though the etiology remains obscure. Certainly one can conclude as of now that regional ileitis is not related to tuberculosis and is clinically different from sarcoidosis. No single causative bacterial agency can be implicated with regularity.

The author discusses various theories regarding the pathologic mechanism in the creation of ileitis. For the first time a concept of the life cycle of the disease emerges. It is characterized by a consistent anatomical distribution, a typical clinical course, a progressive life history, typical complications (fistulas and obstruction) and favorable response to surgical treatment. In gross appearance, regional ileitis has definite characteristics that distinguish it from granulomas elsewhere in the alimentary tract. However, the histologic microscopy of the disease is non-specific. Crohn discusses two pathologic types suggested by Pemberton and Brown, (1) the localized group, which may and does progress to stenotic fibrosis, remains stationary and may lead to intestinal obstruction. This type is favorable to surgery; (2) the second group is scattered, progressive, in the nature of mucosal and submucosal lesions, and yields the majority of the disappointing end results of surgical intervention.

Under its clinical features, Crohn discusses those which are specific and those which are general. Most of the cases are not recognized until they have been symptomatic for one to five years or longer. This alone indicates how much the book is needed. The patients are not as toxic as those with ulcerative colitis. The two outstanding features in the physical examination of the cases of regional ileitis are: (1) an abdominal mass and (2) evidence of fistula formation, external and internal. The precise data on fistula formation in regional ileitis must be astonishing to physicians unfamiliar with the disease. Crohn makes the statement that, as a generalization, suppurative perianal fistulas in the presence of diarrhea indicate a pathologic process elsewhere in the intestinal tract. The course in regional ileitis is precisely analyzed; three variations in the course are considered.

The chapter on the roentgenologic study of regional ileitis has excellent illustrations. Early and late roentgen signs are mentioned and emphasis is placed on the string-sign as an almost pathognomonic finding. In many cases roentgenologic data of ileitis are completely missing and yet the clinical data are so convincing that the diagnosis must be adhered to in the absence of confirmatory roentgen signs. Actually, the diagnosis of regional ileitis is essentially a clinical one. The significance of the perianal fistulas cannot be overlooked.

Considerations regarding therapy pose an open question as to whether any conservative treatment is warranted. Crohn outlines the indications for such therapy. When it comes to surgical relief of the disease a complicated and rapidly changing picture is presented with the evidence favoring a single stage operation, namely, ileo-transverse colostomy, with transection of the ileum, as a sufficient procedure to induce cure. However, there is a growing realization of the increasing evidence of recur-

is anidrosis and was used by Hippocrates; it is often spelt anhidrosis, because it comes from *hidrōs*, sweat. In medical writings today it is common to find it misspelt anhydrosis; but one is shocked to find that Dr. Pepper condones this spelling and derives the word from *hydor*, water. This is the more amazing because, in a later section, we find "hidrosis" and other words compounded from *hidros* correctly treated.

This is the first book of its kind that has appeared on the medical scene. Its conception is so laudable, and the standards of accuracy and clarity which the text for the most part maintains are so high, that it is beyond the range of serious criticism. It is a book which every student, without exception, should own. And many fully fledged physicians may wish to avail themselves of this handy text, feeling with propriety that many a medical

". . . word is too often profaned  
For me to profane it."

H. J. L. M.

*Diseases of the Liver, Gallbladder and Bile Ducts.* 2nd Ed., revised. By S. S. LICHTMAN, M.D., F.A.C.P. 1135 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1949. Price, \$18.00.

This monumental compilation of the literature on diseases of the liver is the only work of its kind currently extant in the English language. It should, therefore, be carefully reviewed and appraised as a specialized textbook which presents the detailed statements of the findings of many authors. It is very valuable—particularly to those workers interested in finding out who wrote what about one phase or another of liver disease. However, the author has leaned over backwards in his desire to be complete and therefore frequently is contradictory in his statements. An example is the statement on page 425 that "Post-serum hepatitis is clinically indistinguishable from infectious hepatitis save for fairly consistent differences in the mode of onset"—compared with page 428, "The onset in an outbreak following yellow fever vaccination was almost indistinguishable from the infectious group."

In the discussion of liver abscess, the first cause is listed as bacillary dysentery, then the statement is made that the solitary liver abscess is often referred to as tropical liver abscess, and this in turn is due to amebic infection. The desire not to leave anything out leads to paragraphs such as that on page 536 where every conceivable factor is listed under "underlying causes" for cirrhosis—alcohol or syphilis figured in the majority of cases. In special types of cirrhosis, gall stones, chronic heart failure, Graves' disease, and abnormal blood pigments may operate as specific underlying causes. Other causative factors include tuberculosis, diabetes, infections including measles, scarlet fever, typhoid. . . . Perhaps most of the trouble here is in semantics—the use of the word "cause" instead of "frequently associated conditions."

And so one comes to the chief criticism. The author has not taken the time to make this a shorter book. There is no need for five pages of discussion of the supposed catarrhal origin of infectious hepatitis which the author correctly discards, and perhaps no need for a whole separate sub-heading on hepatolienal fibrosis of Banti's syndrome (page 673) when at the outset the author himself says it is presented for historical interest and the sake of completeness. This is particularly true since on page 585 the author has given a good summary of portal hypertension and its relation to splenomegaly, etc. Such things are, however, easier to find and criticize than cure, and should not be emphasized as against the general merit of this valuable compilation. It can be highly recommended as a source book and review.

F. B. B.

## BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Electrocardiographic Technique: A Manual for Physicians, Nurses and Technicians.* By KURT SCHNITZER, R. T., M.D. 96 pages; 16 × 23 cm. 1949. Grune & Stratton, New York. Price, \$3.50.

*Industrial Toxicology.* By LAWRENCE T. FAIRHALL, Scientist Director, Public Health Service, Federal Security Agency, etc. 483 pages; 23.5 × 15.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$6.00.

*Industrial Toxicology.* 2nd ed. By ALICE HAMILTON, M.D., Assistant Professor Emeritus of Industrial Medicine, Harvard School of Public Health, Boston, and HARRIET L. HARDY, M.D., Physician to the Division of Occupational Hygiene, Massachusetts Department of Labor and Industries, etc. 574 pages; 21 × 14 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$7.50.

*Patología Psicosomática.* By J. ROF CARBALLO. Prologo by PROF. C. JIMÉNEZ DÍAZ. 817 pages; 25.5 × 18 cm. (paper-bound). 1949. Editorial Paz Montalvo, Madrid, Spain.

*The Skin Problem Facing Young Men and Women.* By HERBERT LAWRENCE, M.D., Diplomate, American Board of Dermatology. 70 pages; 23 × 15 cm. (paper-bound). 1949. Timely Publications, San Francisco. Price, \$1.50.

*Stomach Disease as Diagnosed by Gastroscopy.* By EDDY D. PALMER, A.B., M.S., M.D., Major, Medical Corps, United States Army. Formerly Chief, Gastrointestinal Section, Walter Reed General Hospital, Washington, D. C. 200 pages; 26.5 × 18 cm. 1949. Lea & Febiger, Philadelphia. Price, \$8.50.

*Treatment in Proctology.* By ROBERT TURELL, B.S., M.D., Attending Proctologist, Hillside Hospital, etc. With a chapter on Psychosomatic Problems by LOUIS LINN, M.D. 248 pages; 23.5 × 15.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$7.00.

*The Value of Hormones in General Practice.* By W. N. KEMP, M.D., Vancouver, B.C. 115 pages; 27.5 × 21 cm. (loose-leaf, paper-bound). 1949. Burgess Publishing Company, Minneapolis. Price, \$3.00.

*You and Your Fears.* By PETER J. STEINCROHN, M.D., F.A.C.P. Introduction by C. CHARLES BURLINGAME, M.D., F.A.C.P. 224 pages; 20 × 13.5 cm. 1949. Doubleday & Company, Inc., Garden City, New York. Price, \$2.50.

## A.C.P. POSTGRADUATE COURSES

The American College of Physicians' Bulletin of Postgraduate Courses was published during July and distributed to all members of the College and to non-members on the mailing list.

Course No. 1, CARDIOLOGY, was given at the National Institute of Cardiology of Mexico, from August 15 to 26, with a registration of 25 physicians. Dr. William Dock, F.A.C.P., Professor of Medicine at Long Island College of Medicine, Brooklyn, was a Guest Professor from the United States, and Dr. George Morris Piersol, M.A.C.P., Secretary-General of the College, was the official representative of the Board of Regents. The course was unique in many respects inasmuch as it was organized so that all instruction was concluded at 1:00 p.m. daily, giving the rest of the day for sightseeing trips and a week-end for a more extensive trip to Taxco. The type or method of instruction was particularly suitable to older individuals who find close concentration on continuous didactic lectures tiring, in that this course provided an hour of didactic instruction followed by an hour in the wards and laboratories. All instruction was given in English and the whole course was conducted on a high plane of excellence.

Other courses on the schedule are:

Course No. 2, GASTRO-ENTEROLOGY, October 10-14, University of Chicago School of Medicine, Chicago, Ill., Walter L. Palmer, M.D., F.A.C.P., Director.

Course No. 3, CLINICAL NEUROLOGY, October 17-21, Jefferson Medical College of Philadelphia, Philadelphia, Pa., Bernard J. Alpers, M.D., F.A.C.P., Director.

Course No. 4, PRECLINICAL SCIENCE IN INTERNAL MEDICINE, October 24-29, Washington and St. Louis Universities, St. Louis, Mo., W. Barry Wood, M.D., F.A.C.P., and Ralph A. Kinsella, M.D., F.A.C.P., Directors.

Course No. 5, RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE, November 14-19, Massachusetts General Hospital, Boston, Mass., Howard B. Sprague, M.D., F.A.C.P., and Edward F. Bland, M.D., Directors. This course is definitely limited to 100 registrants. The course is more than half filled and it is probable that it will be over-subscribed with the result that few, if any, non-members can be accommodated.

Course No. 6, BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO INTERNAL MEDICINE, November 28-December 2, University of Wisconsin Medical School, Madison, Wis., William S. Middleton, M.D., F.A.C.P., and Karver L. Puestow, M.D., F.A.C.P., Directors. This course is registered to capacity and no new applications can be accepted.

Course No. 7, BLOOD DYSCRASIAS, December 6-10, Medical College of Alabama, Birmingham, Ala., James B. McLester, M.D., F.A.C.P., Director.

Course No. 8, THE PHYSIOLOGICAL APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES, December 5-10, University of Southern California School of Medicine, Los Angeles, Calif., George C. Griffith, M.D., F.A.C.P., Director.

---

 NEW GROUP OF A.C.P. RESEARCH FELLOWS BEGIN WORK

The following Research Fellows, selected by the Committee on Fellowships and Awards and the Board of Regents during November, 1948, are now launched on their program of work as indicated. The selection of Research Fellows for 1950-51 will take place at a meeting of the Committee and the Board of Regents on November 12-13, 1949.

*Dr. Stefan S. Fajans*—investigative work in the field of determination of physiological mechanisms capable of stimulating or depressing the Islets of Langerhans—under

DOUGLAS M. GORDON, M.D., F.A.C.P., Ponca City. Collagen Fiber Diseases. WILLIAM S. MIDDLETON, M.D., F.A.C.P., Madison, Wis. Clinical Pathological Conference. HUGH JETER, M.D., F.A.C.P., Oklahoma City; FELIX PARK, M.D., F.A.C.P., Tulsa.

---

### A.C.P. DIRECTORY, 1949

It had been anticipated that the new and revised Directory of the American College of Physicians would be ready for distribution on or about October 1, 1949. Some slight delay, unavoidable, due to termination of services of one of the editors, may be anticipated, but it is hoped that the Directory will be completed and delivered to all who placed orders therefor before November 1, 1949.

---

### MEETINGS, A.C.P. COMMITTEE ON CREDENTIALS

The Committee on Credentials of the American College of Physicians will meet at the College Headquarters on November 12, 1949, and on or about March 18-19, 1950, and at Boston, Mass., on April 15, 1950.

Regulations of the Board of Regents prescribe that proposals of candidates must be filed sixty days in advance of action. This notice is published for the aid and direction of members who have candidates to propose.

---

### TWENTY-SECOND GRADUATE FORTNIGHT OF THE NEW YORK ACADEMY OF MEDICINE

The Twenty-second Graduate Fortnight of The New York Academy of Medicine will be held at the Academy building, 2 E. 103d St., October 10-21, 1949, and the theme of the Fortnight will be "Advances in Diagnostic Methods." Dr. Louis J. Soffer, F.A.C.P., is Chairman of the Committee and Dr. Mahlon Ashford, F.A.C.P., of the Academy is the Secretary. Numerous other Fellows of the American College of Physicians are members of the Committee or are participating in the program. A comprehensive exhibit devoted to advances in diagnostic methods will form a part of the program. The registration fee is \$5.00; programs are available through the Academy.

---

### THIRD INTER-AMERICAN CONGRESS OF RADIOLOGY

The Third Inter-American Congress of Radiology will be held in Santiago, Chile, from November 11-17, 1949. The Government of Chile has lent the official patronage of the University of Chile. Hotel Crillon will be the headquarters. There are four main divisions of the program: "Radiological Exploration of the Cardiovascular System with Opaque Material"; "Diagnosis and Simple Radiological Explorations of the Skull"; "Radiation Treatment of Cancer of the Tongue"; and "Radiation Treatment of Cancer of the Cervix." Dr. James T. Case is the United States Regional Secretary of the Executive Committee. All communications concerning the meeting should be addressed to Room 1421, 55 E. Washington St., Chicago 2, Ill.

---

The 1950 Assembly of the Interstate Postgraduate Medical Association of North America will be held at the Hotel Stevens, Chicago, November 6-9, 1950.

---

The 12th Annual Symposium of the Duke Medical School will be held at Durham, N. C., Thursday, Friday and Saturday, October 13, 14 and 15. The general subject will be the "Basis of Disease." Among the guest speakers will be Drs. Stanley Brad-

## OBITUARIES

## DR. WILLIAM GERRY MORGAN, M.A.C.P.

1868-1949

With the sudden death of Dr. William Gerry Morgan, on the seventh of July, 1949, at Washington, D. C., the American College of Physicians lost one of its few remaining charter members. The news of his unexpected death brought deep sorrow to Dr. Morgan's many devoted friends in the College, particularly to those members of the Board of Regents and the Board of Governors with whom he had worked so intimately for so many years.

Dr. Morgan was born in Newport, N. H., on May 2, 1868. After completing his preliminary education at Fryeburg, Maine, he entered Dartmouth College, where he received his B.S. in 1890. Three years later he received his M.D. from the School of Medicine of the University of Pennsylvania, Philadelphia. After serving as Resident Physician at the Reading (Pa.) Hospital for one year, Dr. Morgan entered upon the private practice of medicine in Houston, Tex. He went to the southwest where the climate was less severe, because of his health. A year later, in 1895, he decided not to cast his lot with the growing community of Houston, but to return to his ancestral New England. Between 1895 and 1899 he carried on a private practice at Southport, Conn. The ambitious and energetic spirit of Gerry Morgan was not content with the limitations of a private practice in New England. After his health improved, he determined to devote his energies to the then newly developed specialty of Gastro-enterology. He entered upon a course of postgraduate work under Dr. Max Einhorn, F.A.C.P., at the New York Post-Graduate Medical School, following which he established himself in Washington, D. C. The wisdom of his decision was borne out by the successful career which he followed in that capitol city for half a century. It was not long after he moved to Washington before he was recognized as the outstanding Gastro-enterologist in that part of the country and a wise consultant. Professional recognition came to him when in 1904 he was appointed Professor of Gastro-enterology at Georgetown University School of Medicine, an appointment which he held with distinction throughout his entire life. He was Dean of the Medical School of Georgetown University from 1931-35, and in addition to this served as a Regent of the University for many years. Dr. Morgan's success in his special field of medicine was in no small measure due to the broad medical training which he obtained early in his career as a general practitioner. Although he was an ardent and enthusiastic student of Gastro-enterology, he never neglected the broader fields of medicine. Dr. Morgan was a Diplomate of the American Board of Internal Medicine. His success as a diagnostician was due to his skill in physical diagnosis, a keen understanding of patient psychology and an ability to properly evaluate modern diagnostic procedures in medicine. His interest in all phases of the practice of medicine, and particularly his personal attention to his patients were outstanding traits that dominated his professional life.

Dr. Morgan had never allowed the exacting demands of a large and important practice to interfere with his interest in the academic side of medicine. He was a con-



DR. WILLIAM GERRY MORGAN



well balanced judgment earned for him the friendship and devotion of all who were thrown with him. The affection in which he was held was nowhere better exemplified than in the unfailing devotion which was shown him by all those who were associated with him in any capacity. His loss will be keenly felt and deeply regretted by his host of friends in all walks of life. No group, however, will feel his loss more keenly or miss him more than those who were privileged to work with him for so many years in the American College of Physicians. Dr. Morgan is survived by his widow, Mrs. Cora Morgan, and three daughters, Mrs. Myra Stump, Mrs. Ruth Hardison and Mrs. Gerry Wellborn, each of whom is the wife of a Rear Admiral in the U. S. Navy. The Officers, the Board of Regents, the Board of Governors and Fellows of the American College of Physicians extend to Dr. Morgan's family their heartfelt sorrow, over this irreparable loss which they have sustained.

GEORGE MORRIS PIERSOL, M.D., F.A.C.P.,  
Secretary-General, ACP

### DR. MAYO HAMILTON SOLEY

Born in Malden, Mass., April 14, 1907, Mayo Hamilton Soley was reared in the New England environment. He graduated from Bowdoin College in 1929, and from the Harvard Medical School in 1933. After serving twenty months as a House Officer at the Massachusetts General Hospital on the Medical Service, from July 1933 to February 1935, Mayo came to the University of California Medical School as a special graduate student in Medicine. For the next thirteen years, to July 1, 1948, Mayo progressed rapidly from positions as Research Assistant in Medicine, Instructor in Medicine and Physiology, Instructor in Medicine and Pharmacology, Assistant Professor of Medicine and Pharmacology, Associate Professor of Medicine and Pharmacology, and, on July 1, 1947, was promoted to a professorship in Medicine. For two years, 1942-44, Mayo served as Chairman of the Division of Pharmacology, succeeding Chauncey D. Leake and he lectured also in the College of Pharmacy. From 1944 to 1948, Mayo was Assistant Dean of the Medical School. In addition to a succession of appointments on the visiting staff of the University of California Hospital, Mayo served as Consulting Pharmacologist at the San Francisco Hospital, the Langley Porter Clinic and the Letterman General Hospital.

Dr. Soley became a Fellow of the American College of Physicians in 1948. He was a member of numerous and important medical societies, which are listed to show his wide range of interests and contributions: California Medical, American Medical, American Heart and California Heart Associations, Association for Study of Internal Secretions, American Society for Clinical Investigation, American Association for the Advancement of Science, American Physiological Society, Society for Experimental Biology and Medicine, Sigma Xi, California Academy of Medicine, American Federation for Clinical Research, Western Society for Clinical Research (Vice-President, 1946-47; President, 1947-48), and American Association for Study of Goiter.

It will be noted that Dr. Soley's rise in academic rank was spectacular. He brought to his work a scholarly and inquiring mind. His application to all problems in his wide field of interest was beyond the reach of most of us. He was a gifted teacher, a sound, careful research worker, who was at his best in collaboration with others. His interest in students was noteworthy. Many students came to him for help and guidance in professional and personal matters, and he inspired all of them to seek greater heights of accomplishment.

Dr. Soley's ability as an administrator and student advisor led to his selection as Assistant Dean. In this capacity he had an opportunity which prepared him for his last position, at The State University of Iowa College of Medicine.

## DR. ALEXANDER L. LOURIA

Dr. Alexander Leon Louria, of Brooklyn, N. Y., died on May 22, 1949. He was born in Russia in 1890 and came to this country in 1896. He received his B.S. and his M.D. degrees from Columbia University, in 1910 and 1913. He served an internship in the Jewish Hospital, Brooklyn, from 1913 to 1915, and spent some time in 1920 and 1921 in postgraduate medical study in Germany. He became a member of the staff of Jewish Hospital, and at the time of his death was Clinical Professor of Medicine in the Long Island College of Medicine.

Dr. Louria was elected to Fellowship in the American College of Physicians in 1946. He was a former Trustee of the Medical Society of the County of Kings, and a past-President of the Williamsburg Medical Society.

Dr. Louria was one of the highly respected physicians in Brooklyn, and his untimely death is recorded with regret.

ASA L. LINCOLN, M.D., F.A.C.P.,  
Governor for Eastern New York

## DR. VICTOR FRANCIS CULLEN

Victor Francis Cullen, M.D., F.A.C.P., of Baltimore, Md., died on March 9, 1949. Born in Maryland on September 5, 1881, Dr. Cullen was a graduate of Rock-Hill College and the Johns Hopkins University School of Medicine. He later received the LL.D. degree from Mount St. Mary's College, Emmitsburg. Dr. Cullen served as interne and resident in St. Joseph's Hospital, Baltimore, became superintendent and medical director of the Maryland Tuberculosis Sanatorium in 1908 and served in this capacity and later as superintendent of the Tuberculosis Sanitaria of Maryland until 1946, when he retired.

Dr. Cullen was a Diplomate of the American Board of Internal Medicine. He became a Fellow of the American College of Physicians in 1930. He was a former president of the Medical and Chirurgical Faculty of Maryland and a former president and director of the National Tuberculosis Association.

Dr. Cullen was widely and affectionately known to the medical profession of Maryland. Though his administrative responsibilities were heavy, he made himself constantly available as a consultant in pulmonary disease to practitioners throughout the state. His interests in medicine extended beyond his special field. He gave unselfishly of his time as a prominent member of the Committee on Medical Care to the development of the state supported program of medical care for the indigent and medically indigent in the rural counties of Maryland. A man of high ideals, great generosity and untiring energy, he spent his strength for others and in return was much beloved.

## DR. RALPH PEMBERTON

With the death of Dr. Ralph Pemberton on June 16, 1949, the College has lost one of its old and distinguished Fellows.

Dr. Pemberton's medical interests were varied. *Internal medicine, neurology and chemistry* claimed his interest at various periods of his medical life. It was really his interest in chemistry which led him into the study of arthritis, the subject with which his name will always be associated. It is altogether proper to say that he played an important role in introducing into the study of this subject the orderly, integrated, and intensive investigation which it is now receiving.

Dr. Pemberton was born in Philadelphia on September 14, 1877. He graduated in medicine from the University of Pennsylvania in 1903. In 1911 and 1912 he did postgraduate work in Germany. Incidentally, almost the last thing that he wrote was

# ANNALS OF INTERNAL MEDICINE

---

VOLUME 31

OCTOBER, 1949

NUMBER 4

---

## THE USE OF BAL (BRITISH ANTI-LEWISITE) IN THE TREATMENT OF THE INJURIOUS EF- FECTS OF ARSENIC, MERCURY AND OTHER METALLIC POISONS \*

By WARFIELD T. LONGCOPE, F.A.C.P., and JOHN A. LUETSCHER, JR.,  
*Baltimore, Maryland*

BAL (which stands for British Anti-Lewisite) or 2,3-dimercaptopropanol is a chemical found by Stocken and Thompson while working in Professor Peters' laboratory in Oxford, to be an effective antidote to Lewisite. This discovery made during the war represents the culmination of a long series of important investigations carried on for many years by several investigators, but especially by Professor Peters and his associates in Oxford.

For some time it had been known that the injurious effect of arsenic depends upon its attachment to the sulfhydryl groups of cellular proteins thus interfering with the function of essential enzymes which require the free sulfhydryl grouping for their action. Previous efforts had been made, particularly by Voegtlin<sup>1</sup> to counteract the injurious effects of arsenical intoxication with sulfhydryl containing chemicals such as cysteine and glutathione but these proved only partially effective. The secret of the success obtained by Stocken and Thompson<sup>2,3</sup> lay in the fact that BAL which is a dithiol formed a compound with arsenic which was non-toxic and much more stable than the compounds resulting from the action of the mono-thiols.

There is not time, nor have I the special knowledge even to outline the brilliant series of investigations by Professor Peters and his associates and others which finally led to the discovery of BAL, but those interested in this phase of the subject can obtain much information from the reviews by Peters and Stocken,<sup>4</sup> and by Waters and Stock<sup>5</sup> as well as by a recent lecture of Professor Peters<sup>6</sup> in the Proceedings of the Royal Society of Medi-

---

\* Presented at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., April 1, 1949.

From the Medical Clinic of The Johns Hopkins University and Hospital.

symptoms of intoxication appeared within a few minutes, reached their height within 10 to 30 minutes and then subsided. Tye and Siegel<sup>14a</sup> state that the unpleasant symptoms caused by BAL were relieved in one patient by the administration of 0.6 c.c. of 1-1,000 solution of epinephrine hydrochloride intramuscularly and were prevented in this patient and in one other by an oral dose of 25 mg. or 50 mg. of ephedrine given one-half hour before the injection of BAL.

The symptoms are as follows :

TABLE I  
Symptoms of Poisoning by BAL

1. Nausea and vomiting.
2. Headache.
3. Burning sensation of lips, mouth, etc.
4. Feeling of constriction of throat, chest and hands.
5. Conjunctivitis, tearing and salivation.
6. Tingling of hands.
7. Burning sensation of penis.
8. Sweating of forehead and hands.
9. Abdominal pain.
10. Tremors and shakiness.
11. Lower back pain.
12. Elevation of blood pressure.

Our experience<sup>15</sup> in treating post arsphenamine dermatitis by BAL was somewhat limited for we had only 15 cases, but the results were similar to those of Eagle and Magnuson<sup>10</sup> who reported 88 cases and of Carleton, Peters<sup>11, 12</sup> etc. who have now recorded their results in a total of 74 cases.

In general it may be said that on the schedule of dosage employed the results have been very satisfactory in the majority of cases, with dramatic improvement in many instances. Often within 24 to 48 hours after the intramuscular injections are started, even in severe cases, the erythema, edema and itching of the skin subside, while the weeping vesiculitis becomes dryer. In the early stages scaling may set in, and in the more advanced cases exfoliation may actually increase. Occasionally progressive recovery takes place with surprising rapidity, but usually even when the course is favorable it is several days before healing of the skin is complete. Nevertheless five of our patients were completely well within 12 days. Eagle states that of 51 patients suffering from a severe form of exfoliative dermatitis, 40 showed improvement five days after BAL therapy was instituted and the majority had "recovered" by the fifteenth day. Carleton and Peters in their recent paper<sup>12</sup> state that the response to treatment was beneficial in 70 per cent of their cases, the mean duration of the dermatitis being 21.5 days in contrast to a control series not treated by BAL in which it was 62.5 days. In a control series collected by us the average duration of the dermatitis was 67.3 days.

The amount of arsenic employed in the treatment of syphilis, the occurrence of dermatitis in hypersensitive patients after small doses of the arsenical and the presence of secondary infection of the skin all seem to have

admitted to the hospital. A few were in collapse, several were vomiting blood and suffering from abdominal pain and bloody diarrhea. A few showed superficial ulceration of the gums and fauces or bluish black discoloration of the tongue. Serious uremia developed in four patients, two of whom recovered. Two of the 61 patients died, one being the first patient treated with inadequate amounts of BAL, 13 hours after the ingestion of at least 1 gram of bichloride, the other was a woman treated five and one-half hours after swallowing at least 2 grams of bichloride. Both died in uremia.

Of the 59 patients who recovered, improvement occurred in all but two with astonishing rapidity. Nausea, vomiting, diarrhea and abdominal pain were relieved within 24 to 48 hours, and even the most severely poisoned patients were symptomatically well within three to four days. There were no complications or residua such as persistent diarrhea, anemia, loss of weight or ulceration of the buccal mucous membrane. The two patients in whom convalescence was prolonged had persistent renal insufficiency, complicated in one by pneumonia.

TABLE II  
HgCl<sub>2</sub> Poisoning  
61 Cases treated with BAL

Grams HgCl <sub>2</sub> Dose	Patients	Recovery	Death
0.5	20	20	0
1.0	18	17	1
1.5	12	12	0
2.0+	11	10	1
	61	59	2

It soon became evident that there were at least two important factors that might determine the outcome in these patients. One was the period intervening between the ingestion of bichloride and the start of treatment by BAL and the other, the amount of BAL administered and the duration of treatment.

Prompt institution of treatment by BAL is of paramount importance. This becomes evident when the outcome is compared in 38 patients who had taken from 1 gram to 20 grams of bichloride and were treated with BAL within four hours to a similar control group of 86 patients not treated with BAL but by the older conventional methods. There were no deaths in the 38 receiving BAL and 27 deaths in the 86 without BAL. A dose of 3 grams or more of bichloride killed eight of nine patients not treated by BAL while after prompt treatment of BAL all of four patients survived 3 to 20 grams of the poison.

One of the deaths in the series treated with BAL occurred in a woman who had swallowed at least 1 gram of bichloride 13 hours before admission, and had severed the arteries in both wrists. She also received insufficient amounts of BAL. The other death was in a woman who had swallowed 2

tremities following a single injection. One patient complained of flushing of the face, fullness in the head, sweating, shooting pains in the arms, legs and burning in the epigastrium after a dose of 300 mg. of BAL. Two women were observed to have cardiac irregularities due to extrasystoles following single doses of 150 mg. of BAL. A great many patients showed a moderate elevation of blood pressure within the first 24 or 48 hours after admission, but it is questionable as to whether this was due to BAL.

The tolerance that these patients appeared to show for BAL was interpreted as being due to the fact that the large quantities of mercury present in the body combined with all or most of the BAL which was injected. As the complex is rapidly eliminated, and devoid of toxic properties, both mercury and BAL were rendered inert.

Adjuvant treatments have been employed. Practically all patients were subjected to gastric lavage with sodium formaldehyde sulfoxylate on admission and were given large quantities of fluid during their course in the hospital. Blood transfusions were given to a few patients who were admitted in shock.

It has recently been shown by Sussman and Schlack<sup>21</sup> that BAL annuls completely the diuretic effect of mercurhydrin, and by Long and Farah<sup>22</sup> that it combats the acute toxicity of salyrgan in animals.

Efforts have been made to extend the use of BAL to control the poisonous effects of other metals. Favorable results have been reported in the treatment of several of the untoward complications of gold therapy. These include dermatitis, stomatitis, thrombopenia, purpura and granulocytopenia.<sup>23, 24, 25, 26, 27, 28</sup>

There is some experimental evidence to indicate that BAL may have a beneficial effect in poisoning by antimony (Braun, Lusky and Calvery<sup>29</sup>; Gammill, Southam, etc.<sup>30</sup>; Eagle, Germuth, etc.<sup>31</sup>).<sup>20a</sup>

Lead is a common form of metallic poisoning and it was hoped that BAL might prove to be a valuable remedy for this form of intoxication. Experimental investigations have, however, shown as was observed first by Braun, Lusky and Calvery<sup>29</sup> that exactly the opposite result takes place. For the administration of BAL to animals acutely poisoned by lead, actually enhances its toxic effect. This may be due, according to Germuth and Eagle<sup>32</sup> in part at least to the fact that the BAL-lead complex proved in their experiments to be almost as toxic to rabbits as lead itself. They have shown, nevertheless that a single dose of BAL injected into rabbits, which had previously received lead acetate, did increase the urinary excretion of lead 11 to 40 fold within two hours. Ryder, Cholak and Kehoe<sup>33</sup> administered BAL to men suffering from lead poisoning and following single doses noted an increase in the urinary excretion of lead which reached its peak within one to two hours. The injections of BAL did not have any beneficial effect upon the symptoms of lead poisoning in these individuals. We have had the same experience in one patient suffering from anemia and intestinal colic due to lead poisoning who, after each of two courses of BAL, excreted large

## BIBLIOGRAPHY

1. VOEGTLIN, C., DYER, H. A., and LEONARD, C. S.: On the mechanism of the action of arsenic upon protoplasm, *Pub. Health Rep.*, 1923, xxxviii, 1882.
2. STOCKEN, L. A., and THOMPSON, R. H. S.: British Anti-Lewisite. I. Arsenic derivatives of thiol proteins, *Biochem. Jr.*, 1946, xl, 529.
3. STOCKEN, L. A., and THOMPSON, R. H. S.: British Anti-Lewisite. II. Dithiol compounds as antidotes for arsenic, *Biochem. Jr.*, 1946, xl, 535.
4. PETERS, R. A., STOCKEN, L. A., and THOMPSON, R. H. S.: British Anti-Lewisite (BAL), *Nature*, London, 1945, clvi, 616.
5. WATERS, L. L., and STOCK, C.: BAL (British Anti-Lewisite), *Science*, 1945, cii, 601.
6. PETERS, R. A.: Pharmacology and biochemical lesions, *Proc. Royal Soc. Med.*, 1948, xli, 781.
7. LONGCOPE, W. T., and LUETSCHER, J. A., JR.: The use of British Anti-Lewisite in the treatment of poisoning by arsenic, mercury and other metals, *Advances in Internal Medicine*, 1949, iii, 1.
8. EAGLE, H.: The effect of sulfhydryl compounds on the antispasmodic action of arsenic, bismuth and mercury compounds in vitro, *Jr. Pharm. and Exper. Therap.*, 1939, lxvi, 436.
9. EAGLE, H., and MAGNUSON, H. J., and FLEISCHMAN, R.: The systemic treatment of experimental arsenic poisoning (mapharsen, lewisite, phenylarsenoxide) with BAL, *Jr. Clin. Invest.*, 1946, xxv, 451.
10. EAGLE, H., and MAGNUSON, H. J.: The systemic treatment of 227 cases of arsenic poisoning (encephalitis, dermatitis, blood dyscrasias, jaundice, fever) with 2,3-dimercaptopropanol (BAL), *Am. Jr. Syph.*, 1946, xxx, 420.
11. CARLETON, A. B., PETERS, R. A., STOCKEN, L. A., THOMPSON, R. H. S., and WILLIAMS, D. J.: The treatment of complications of arsenotherapy with BAL, *Jr. Clin. Invest.*, 1946, xxv, 497.
12. CARLETON, A. B., PETERS, R. A., and THOMPSON, R. H. S.: The treatment of arsenical dermatitis with dimercaptopropanol, *Quart. Jr. Med.*, 1948, xvii, 49.
13. SULZBERGER, M. B., BAER, R. L., and KANOF, A.: Studies on the toxicity of BAL on percutaneous and parenteral administration, *Jr. Clin. Invest.*, 1946, xxv, 474.
14. MODELL, W., GOLD, H., and CATTELL, M.: Pharmacological observations on BAL by intramuscular injection in man, *Jr. Clin. Invest.*, 1946, xxv, 480.
- 14a. TYE, M., and SIEGEL, J. M.: Prevention of reaction to BAL, *Jr. Am. Med. Assoc.*, 1947, cxxxiv, 1477.
15. LONGCOPE, W. T., LUETSCHER, J. A., JR., WINTROBE, M. M., and JÄGER, V.: The treatment of arsenical dermatitis with preparations of BAL, *Jr. Clin. Invest.*, 1946, xxv, 528.
16. LUETSCHER, J. A., JR., EAGLE, H., and LONGCOPE, W. T.: The effect of BAL on the excretion of arsenic in arsenical intoxication, *Jr. Clin. Invest.*, 1946, xxv, 534.
17. HOLLEY, H. L.: The use of BAL (2,3-dimercaptopropanol) in the treatment of agranulocytosis following intensive arsenotherapy for syphilis, *Ann. Int. Med.*, 1947, xxvii, 231.
18. ARMSTRONG, C. D., FLEMING, W. J., and THALMANN, W. G.: BAL (2,3-dimercaptopropanol) in treatment of massive overdosage with mapharsen, *Calif. Med.*, 1948, lxix, 247.
- 18a. SCHRUMP, A.: BAL therapy of thrombopenic purpura after arsphenamine treatment, *Jr. Am. Med. Assoc.*, 1947, cxxxv, 1152.
- 18b. FRIEDENBERG, S.: Trypanarsamide optic neuritis treated by 2,3-dimercaptopropanol (BAL), *Jr. Am. Med. Assoc.*, 1947, cxxxv, 1072.
19. GILMAN, A., ALLEN, R. P., PHILIPS, F. S., and ST. JOHN, E.: The treatment of acute systemic mercury poisoning in experimental animals with BAL, thiosorbital and BAL glucoside, *Jr. Clin. Invest.*, 1946, xxv, 549.
20. LONGCOPE, W. T., and LUETSCHER, J. A., JR.: The treatment of acute mercury poisoning by BAL, *Jr. Clin. Invest.*, 1946, xxv, 557.

# THE DIVERSITY OF GOUTY ARTHRITIS AND ITS COMPLICATIONS \*

By JOHN H. TALBOTT, M.D., F.A.C.P., *Buffalo, N. Y.*

THE clinical manifestations of gouty arthritis as it is usually seen are well documented and are readily recognized, be they associated with the acute involvement of the joints or the chronic changes. Less well appreciated are the vagaries of metabolic gout which include the unusual aspects of gouty arthritis in addition to the definitive complications which may embrace non-articular structures of the body. Although the malady is a chronic one interspersed with acute exacerbations in all afflicted persons, it may be associated with a great diversity of clinical manifestations. In some patients irreparable joint involvement may be so extensive, especially of the hands and the feet, as to lead to rheumatic invalidism. Less than 5 per cent of the gouty patients seen by us would be so classified.<sup>1</sup> When the disease progresses to this degree the patient is truly an invalid and may be as crippled as a patient with advanced rheumatoid arthritis. Furthermore, rheumatoid arthritis may be associated with gout in an occasional patient. An illustration of crippling gouty arthritis, as well as one with gout plus rheumatoid arthritis, will be discussed below. On the other hand, one encounters occasionally a patient with gouty arthritis who has lived three score and ten years but with no gross irreparable damage to the joints which is specifically attributable to gout. Such patients have acute attacks of joint disease, they respond well to colchicine, but the metabolic affliction is little more than a nuisance at any time and produces no greater injury to the cartilage of the joints than to the cartilage of the ear.

Although involvement of the joints is the identifying characteristic of the malady, during acute episodes as well as after the development of chronic changes, pathologic embarrassment of the kidney and complications associated therewith may produce critical clinical findings and in some patients may lead to death from renal insufficiency. Renal failure is the most important cause of death of gouty patients, irrespective of age, and the only important cause of death prematurely. Chronic renal impairment may go hand in hand with advanced joint disease or it may completely overshadow what appears clinically to be relatively minimal joint involvement. Case

\* Presented at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., April 1, 1949.

From the Departments of Medicine of the Buffalo General Hospital and the University of Buffalo School of Medicine, Buffalo, N. Y.

The researches on gout have been supported by grants from The National Institute of Health, The John Hartford Foundation, New York, N. Y., and the Weed Foundation, Buffalo, N. Y.



delay progression of irreparable damage. The patient is not a physician but his understanding of the disease would command the respect of many members of the profession. The family history is negative for gout but his mother had an elevated concentration of serum uric acid. She died in 1944 of myocardial infarction.

At the age of six, the patient had trouble with his left hip, a diagnosis of tuberculosis of this joint was made and the leg was immobilized for eight months. In retrospect it is believed that the joint trouble most likely was gout and not an infectious process. At least there was no evidence to suggest tuberculosis except the clinical impression, either before or after this event. At the age of 12 there was inflammation of various joints which persisted several days. During the next eight years he noted a

FIG. 2. Roentgen-ray of left foot, patient 1, taken at the age of 25. Many osseous tophi are seen. There is no structural deformity and minimal soft tissue changes.



decreasing interval between acute attacks and by the time he was 21 he had several acute attacks per year. Following subsidence of the acute joints with colchicine therapy, his physical examination was quite negative. Between attacks there was no evidence of joint disease, no limitation of motion, no subcutaneous tophi and no changes in the joints by roentgen-ray (figure 1). He was not long to be spared the chronic stigmata of the disease, however, and within the next 18 months urate tophi appeared on the hands and ears. The first roentgen-ray changes noted in the hands and feet were observed at the age of 23. There were discrete osseous tophi which did not appear to involve grossly the articular spaces. He had frequent attacks of acute arthritis which responded well to colchicine but progression of this disease, clinically and by

is no longer than frequently seen. The number of days per year, however, that he has suffered from acute arthritis is probably the maximum in our experience. This case lends support to the hypothesis that the number of days per year in which the patient is acutely afflicted, influences markedly the degree of permanent involvement. A mild case of gout over a period of years usually means an occasional attack only and little or no serious joint involvement. Per contra, a severe case probably implies many attacks per year and eventually extensive joint involvement.

*Case 2.* H. K., a female with advanced gouty arthritis, had her first joint trouble at the age of 14. During the next 30 years she had one or more attacks of mild to moderate acute gout annually. The family history was positive for gout. Her father had a mild form of the disease. His serum uric acid was 7.7 mg. per cent. At the age



FIG. 5. Cross section of amputated leg, patient 1. Urate deposits have replaced most of the normal structures of the foot.

of 34 she had a bilateral oophorectomy and a hysterectomy. When she was seen first by us at the age of 44 she had extensive subcutaneous deposits of sodium urate and moderate involvement of the bones and joints by roentgen-ray (figure 6). More disturbing from a clinical standpoint was the renal involvement. The urine showed albumin in all samples, the maximum specific gravity of the urine following abstinence from fluid for 12 hours was 1.013 and the excretion of phenolsulphonphthalein dye, 1 c.c. injected intravenously, was less than 8 per cent in the first 15 minutes. The serum uric acid was 8.2 mg./100 c.c. The non-protein nitrogen was 38 mg./100 c.c. During the next five years she developed progressive nitrogen retention and a gradually increasing concentration of uric acid in the serum. At several examinations it was greater than 10 mg. The joint involvement progressed also but her incapacity late in the disease was largely related to renal insufficiency. She died at the age of 49 in uremia.

travenous injection of 1 c.c. The electrocardiogram was normal. A routine chest plate showed one cavity in the right apex and another in the left lower lobe. Two sputum examinations were negative for tubercle bacilli.

He was followed periodically until his death from uremia, four years later. Twenty-one serum uric acid determinations were performed during this period of time. The concentrations varied from 7.9 to 12.6 mg./100 c.c. The non-protein nitrogen concentrations varied from 60 to 150 mg./100 c.c. shortly before death. For a period of a few



FIG. 6. Roentgen-ray of foot of patient 2, at the age of 44. There is narrowing of the joint space of the metatarsal-phalangeal joint and a few osseous tophi. Compare this with figure 3.

months he was thought to have mildly active tuberculosis and sanatorium care was attempted. Because of a profound anxiety neurosis he was discharged home without having received any benefit. His gout progressed slowly but he had no more than three mild to moderate acute attacks per year. The roentgen-rays taken a few months before death showed a few additional changes associated with gouty arthritis. The clinical evidence of chronic joint disease was minimal. The blood pressure at the last admission to the hospital was 164 mm. Hg systolic and 114 mm. diastolic. He died in

impaired ability of the kidney to excrete uric acid, one might expect more extensive deposits of uric acid in bones and soft tissues after a 20-year period of renal dysfunction. The duodenal ulcer, anxiety neurosis and pulmonary tuberculosis were believed to have been unrelated to the gouty arthritis. In the series of patients with gout followed in this clinic, a frequent association of gout and these several maladies has not been observed.

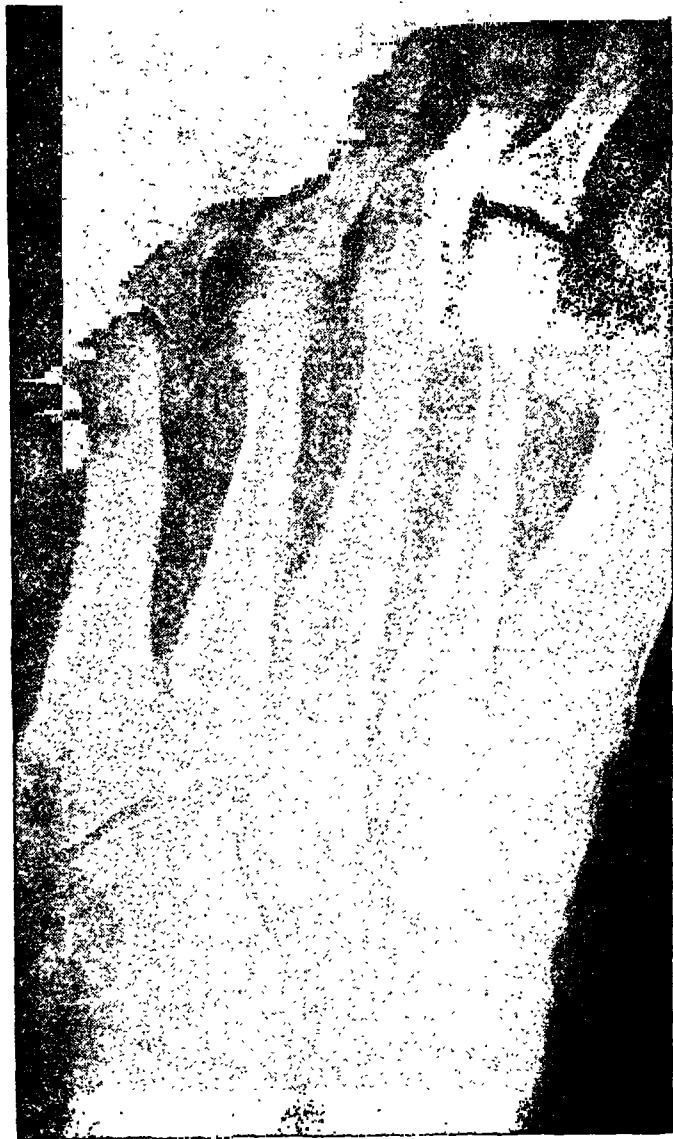


FIG. 8. Roentgen-ray of second, third and fourth metatarsal-phalangeal joint of the right foot of patient 4. Typical osseous tophi are seen.

*Case 4.* B. S., a white male, was seen first at the age of 50. He stated that the first joint symptoms, acute arthritis of the great toes, appeared at the age of 41. During the subsequent six years he had one or more acute episodes each year. The shoulders and knees were the site of attacks as well as the hands and the feet. Colchicine was prescribed in the early years and although it was not taken regularly it helped a great deal when full doses were ingested. He was symptom-free between attacks until the age of 49. At this time he noted persistent limitation of function of

*Comment.* The association of gout and rheumatoid arthritis is an uncommon occurrence; some even deny the association.<sup>2</sup> When it is suspected, a difficult problem in diagnosis and treatment is presented. The development of the two conditions in one patient is probably coincidental and it is not thought that either disease predisposes to the other. The several diagnostic criteria for gout are satisfied in B. S.: history of acute attacks in peripheral joints, response to colchicine and typical roentgen-ray findings nine years after the onset of symptoms. Likewise, the diagnosis of rheumatoid arthritis seems justified on the basis of involvement of central joints, clinical appearance of affected joints, and the pathological examination of the nodule. Colchicine continues to be effective in the treatment of his acute attacks but more important now is the treatment of his presumed rheumatoid arthritis.

*Case 5.* B. C., a white male, was seen first at the age of 59. He denied having had any acute attack of joint disease prior to the age of 56. At the age of 19 he had an injury to his left hand and broke several fingers. They remained in flexion. The first attack of acute arthritis was in the knee which was swollen and red. A diagnosis of 'water on the knee' was made but aspiration was not performed. At the time of admission he complained of severe pain in the right hand that had not responded to hot soaks. On physical examination the blood pressure was 118 mm. Hg systolic and 76 mm. diastolic. There was a small tophus in each ear. The left hand showed the flexion deformity; the right hand was diffusely swollen, red and tender. The rectal temperature was 100.6° F. The physical examination was otherwise negative. The concentration of serum uric acid was 7.9 mg./100 c.c. and non-protein nitrogen 28 mg./100 c.c. The excretion of phenolsulphonphthalein dye was 19 per cent in the first 15 minutes and a total of 66 per cent in two hours after intravenous injection. The routine urine examination was negative. The roentgen-rays of the hands showed a few punched-out areas in the metacarpal-phalangeal joints and the flexion deformities. The roentgenograms of the feet showed minimal changes attributed to gout (figure 9).

In the next four years he took one colchicine pill each day and had three mild attacks of acute gouty arthritis. He died at the age of 63 of an acute myocardial infarct. This was not anticipated in that he had no previous symptoms suggestive of coronary heart disease.

*Comment.* This is an instance of minimal gouty arthritis with the first joint symptoms appearing at the age of 56. When seen less than three months after the first attack he had evidence by roentgen-ray of gout in the joints. The joint involvement was never a serious problem and death was caused by a myocardial infarct. Although the presence of irreparable gouty changes and subcutaneous tophi have been reported in association with the first attack of gouty arthritis, this is not the usual finding. Generally, patients have had joint symptoms for several years before tophi appear or roentgen-ray evidence of osseous tophi is demonstrable. Patient 8 is included to further illustrate this phase of the subject.

*Case 6.* F. P., a white male, was first seen at the age of 62 complaining of acute arthritis in the right foot of four days' duration. At the age of 50 he passed some gravel in his urine following pain in the right flank, chills and fever. He had three more episodes of passing gravel in the following 10 years. In one instance, the gravel

gravel. The level of his serum uric acid varied from 6.2 to 12.4 mg./100 c.c. and the non-protein nitrogen from 28 to 34 mg./100 c.c. Death followed several weeks of cardiac failure from arteriosclerotic heart disease.

*Comment.* The passage of urate stones or gravel by gouty patients is seen occasionally. Hench<sup>5</sup> gives the incidence of gravel or stones as 13 per cent. In at least one other patient in our series, uric acid gravel was passed several years before the onset of joint symptoms. The development of urate stones after onset of joint symptoms does not appear to be directly related to the severity of renal disease. In a limited number of patients, the reverse appears to be true; if urate stones are found, renal impairment is not severe.

Another relevant aspect of urate stones is their spontaneous appearance in persons who do not develop gouty arthritis at some later time. The patients that have been followed for several years who have passed uric acid stones and who have had a normal serum urate have not developed gouty arthritis or an elevated serum urate subsequently. It cannot be denied that each person is not in the pre-arthritic stage of gout and will not develop gouty arthritis in the future. It is the belief of the writer, however, that this will not prove to be a fact and that urate stones do not necessarily mean gout. It is hoped that some investigator will report a long-term study of patients with urate stones who do not have metabolic gout or gouty arthritis at the time of observation. Determination of the urinary excretion of uric acid in such persons would be extremely valuable.

*Case 7.* P. D., a white male, who was first seen at the age of 57, had his initial attack of gouty arthritis in the right great toe at the age of 54. Each year thereafter he had an attack in the shoulders or feet which kept him in bed two or three days. The physical examination was negative except for Dupuytren's contractures of both hands. The urine examination was negative. The serum uric acid was 8.2 mg./100 c.c. The roentgen-rays of the hands and feet showed only one area of diminished density at the base of the proximal phalangeal joint of the right great toe. During the next four years he took one or two colchicine tablets each day as a prophylactic procedure. In this period of time he had one mild attack which was abated with a total of four colchicine tablets and one severe attack which required 12 tablets.

*Comment.* This patient illustrates the typical findings in a mild case of gout. The joint symptoms appear in middle life, the disease is not incapacitating, demonstrable sequelae do not develop and the joint symptoms are controlled with hourly doses of colchicine during acute symptoms and a few colchicine tablets per week in the symptom-free periods.

*Case 8.* P. W., a 45-year old white male, was seen for an unexplained tender left foot which began five weeks before admission following minor trauma to the instep. The patient continued to work for four days but was uncomfortable. He was then forced to use crutches and did not work for 10 days. Low grade symptoms persisted for the next two weeks and he used crutches intermittently. Finally, he was referred to the hospital for injection of the sympathetic nerves. He refused this procedure after admission because he had improved slightly upon bed rest.

On examination the foot demonstrated the cardinal signs of inflammation. The serum uric acid was 7.4 mg./100 c.c. The roentgen-rays of the feet (figures 11 and 12) showed some decalcification in the affected foot only and one area interpreted as

sidered a normal healthy person in all respects except for the metabolic changes associated with gout.

### SUMMARY

Selected items from the medical study of eight patients with gout are presented. They serve to illustrate the diversity of gout and gouty arthritis.

The onset of symptoms, i.e., the first attack of gouty arthritis may appear in the first decade of life or as late as the eighth decade.

At the time of the first attack roentgen-ray evidence of osseous tophi or subcutaneous tophi on inspection usually is lacking.

The passage of urate stones or urate gravel may precede the first attack of gouty arthritis. Urate stones may be passed by persons who do not develop gouty arthritis subsequently.

Renal disease is the most important non-arthritic phase of gout. There appears to be no close correlation between renal involvement and joint involvement. The pathological findings in the kidney of gouty patients are a mixture of several entities.

Rheumatoid arthritis and gout may be observed in the same patient. Each disease must be treated independently. This may be done without aggravating either condition.

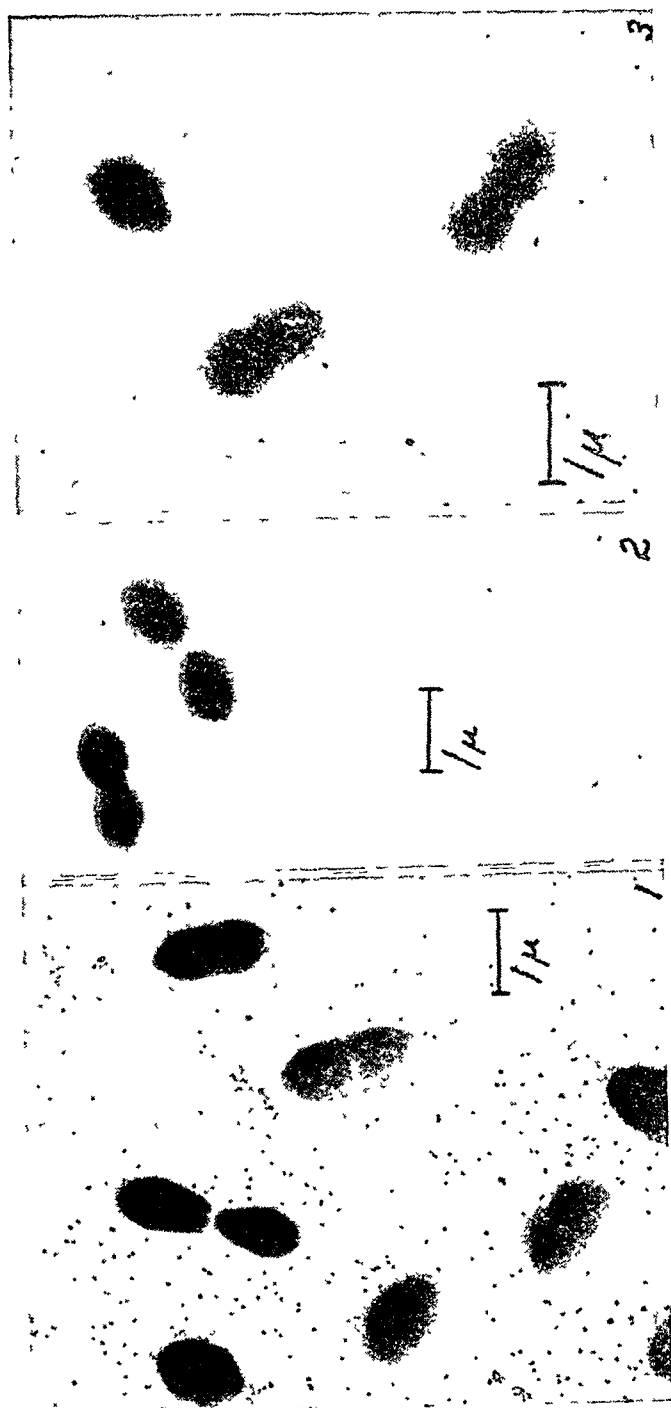
Colchicine 0.5 mg. per hour is recommended for the acute attacks. This dosage should be maintained until onset of gastrointestinal distress. From 10 to 14 doses are usually sufficient. Colchicine is then stopped and Tinct. Camph. Opii. is given.

Between attacks some colchicine is recommended. In patients with frequent attacks of arthritis, one or two colchicine tablets each day is advised. Less severe cases may require but one or two tablets per week.

A balanced diet with a liberal fluid intake seems to produce as satisfactory results in many patients as does rigid dieting.

### BIBLIOGRAPHY

1. TALBOTT, J. H.: Gout, 1943, Oxford University Press, New York.
2. BAUER, W., and KLEMPERER, F.: Gout, in Duncan, Diseases of metabolism, 1942, Saunders, Philadelphia.
3. JACOBSON, B. M.: The uric acid in the serum of gouty and non-gouty individuals: its determination by Folin's recent method and its significance in the diagnosis of gout, *Ann. Int. Med.*, 1938, xi, 1277.
4. COOMBS, F. S., PECORA, L. J., THOROGOOD, E., CONSOLAZIO, W. V., and TALBOTT, J. H.: Renal function in patients with gout, *Jr. Clin. Invest.*, 1940, xix, 525.
5. HENCH, P. S.: Gout, in Cecil, Textbook of medicine, 1947, Saunders, Philadelphia.



1—*Diplococcus pneumoniae*, type 3.

2—*Diplococcus pneumoniae*, type 3 in type 1 serum.

3—*Diplococcus pneumoniae*, type 1 in type 1 serum.

FIG. 1. The pneumococcal capsular swelling reaction. Reproduced from Mump, S., HEINMETS, F., and ANDERSON, T. F.; Jr. Exper. Med., 1943, lxxviii, 327-332. Prints for figures 1 to 4 inclusive furnished by Committee on Materials for Visual Instruction in Microbiology, Society of American Bacteriologists; Dr. Harry E. Morton, Chairman, University of Pennsylvania.



morphologically complete cells with characteristics convenient for direct electron microscopic investigation of the structure and organization of protoplasm in this relatively simple form.

Antibodies have been made visible in combination with the surface structures of bacteria and viruses. Antibodies combine chemically with and form a surface deposit on cell wall and flagella of non-capsulated bacteria<sup>4,73</sup> and on the surfaces of virus particles.<sup>26, 74, 75</sup> In the case of virulent pneumococci, antibodies and other serum proteins permeate and swell the extra cellular capsule.<sup>76</sup>

Certain germicides may readily penetrate the bacterial cell wall and attack the plasma membrane.<sup>77, 78</sup> Antibiotics<sup>30, 79-82</sup> may inhibit cell division and result in morphological aberrations or in bacteriolysis. Morphological difference in the nucleus in phase variants has already been reported.<sup>83</sup> Study by light and electron microscopy of the bacterial nucleus in relation to genetic change and to the action of mutation-inducing physical and chemical agents is a fascinating problem to the threshold of which current advances in the cytology and genetics of microorganisms and the technics of electron microscopy<sup>84-87</sup> have just brought us.

The electron microscope has made a peculiarly valuable contribution to the study of the rickettsiae and viruses, which are near or beyond the limits of resolution of the light microscope. The rickettsiae, viruses of the lymphogranuloma-psittacosis group,<sup>27-29</sup> and the pox viruses<sup>13, 24-26</sup> have been shown to have the structure of very simple cells equivalent to that of tiny bacteria. The cell wall and protoplast may be differentiated, and in vaccinia there has even been described what appears to be a nucleus.<sup>88</sup> The influenza virus, which is quite invisible with the light microscope, has also apparently a surface membrane and inner protoplasm. The particles of bacteriophage, which are often considered as viruses parasitic upon bacteria, are usually tiny sperm-shaped particles containing a head of characteristic shape and a tail. The head of coliphage particles is of complex structure in that it contains a characteristic pattern of granules. The contents of the head, moreover, may be released and leave an empty envelope with tail attached.<sup>89</sup> The currently available evidence strongly suggests that the larger viruses, such as those of lymphogranuloma and psittacosis and of the pock diseases, multiply like bacteria by division, but that the most thoroughly studied bacteriophage particles are synthesized within the bacterial cell. The fact that phage-infection of a bacterial cell imposes a new metabolic pattern on the infected cell and results in the elaboration of multiple new infectious phage particles is a remarkable one, study of which may well afford clues to the understanding of virus-induced neoplasia. Colony-like groups of virus particles have been demonstrated in the cytoplasm of cells of virus-induced neoplasia.<sup>51, 53</sup>

Isolated virus particles under proper conditions have been shown by Wyckoff<sup>22, 23</sup> to form beautiful crystalline arrays in three dimensions. In general it may be said that the problem of visualizing any of the viruses is

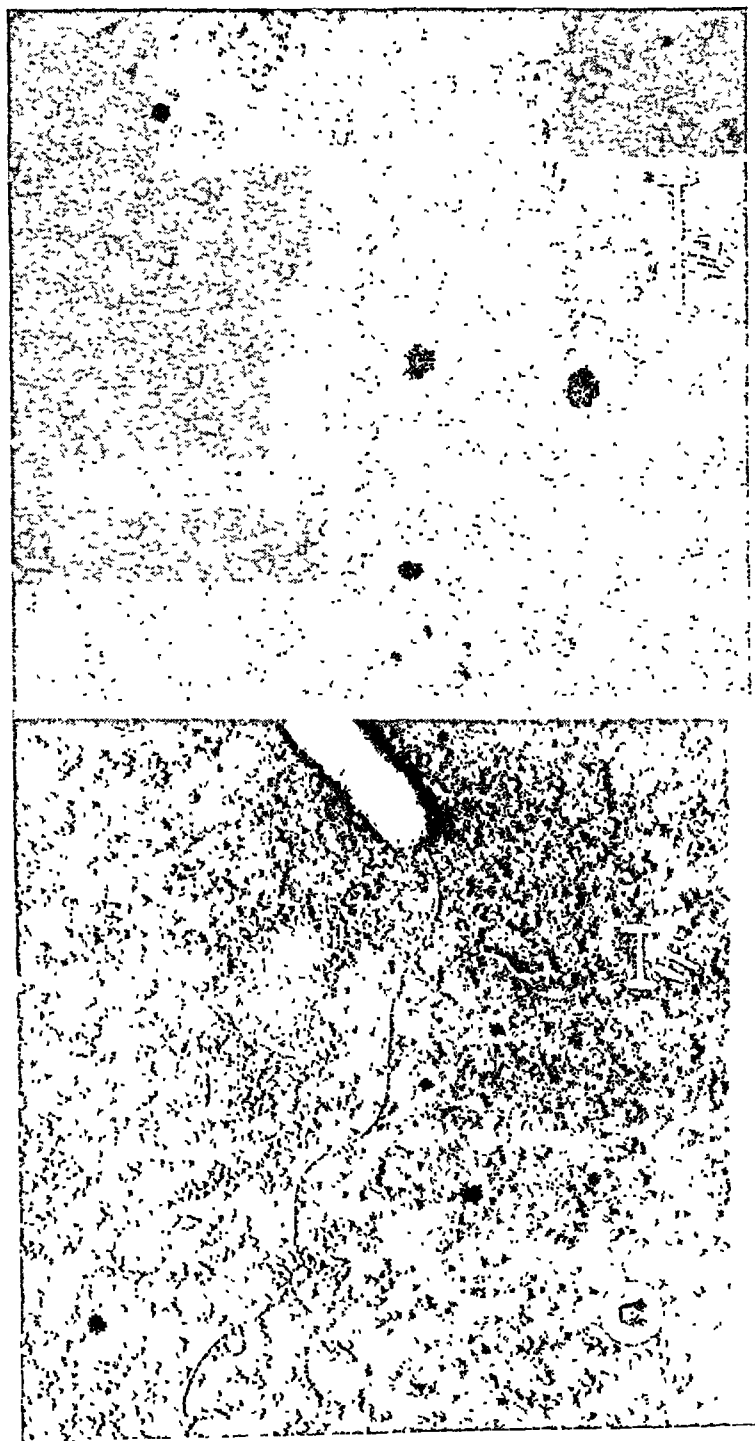


FIG. 4. Rabbit papilloma virus shadowed with gold. In the picture on the left a bacterium with terminal flagellum is included to illustrate minute size of these virus particles. From SHARP, D. G., TAYLOR, A. R., HOOK, A. E., and BEARD, J. W.: *Proc. Soc. Exper. Biol. and Med.*, 1946, lxi, 259-265.

sciences has been broadened steadily by the development of new technics both preparative and instrumental. Tissue culture cells, their components and inclusions are being rendered accessible to investigation through technics under development by Claude and Porter.<sup>50-54</sup> Regularities of internal structures of collagen, muscle, nerve and fibrin fibrils have been revealed through adaptation of fixation, "electron staining" and shadowing procedures.<sup>39-49</sup> Metallic shadow casting<sup>20</sup> has increased contrast and has made possible the imaging of minute structures in three dimensions. Technics of surface replica which have had wide application in metallography, mineralogy, etc. are being applied to the study of biological surfaces.<sup>47, 54, 62, 90</sup>

Incomparably the greatest broadening of applications of electron microscopy has been made possible by the elaboration of methods for cutting thin sections of tissue. Early work by O'Brien and McKinley<sup>91</sup> has been followed by the construction of a high speed microtome<sup>92</sup> capable of cutting sections of the order of  $0.1\ \mu$  in thickness. Studies of such sections of various tissues including neoplasia are appearing.<sup>55-57</sup> Most recently D. C. Pease and R. F. Baker<sup>58, 59, 61</sup> of the University of Southern California, employing double imbedding in collodion and paraffin and a special adapter to the conventional microtome, have cut and made beautiful electron micrographs of sections of liver, muscle, nervous tissue and chromosomes only  $0.05$ – $0.10\ \mu$  in thickness. This technical achievement makes accessible to electron microscopic study the enormous field of the fine structure of normal and pathological tissues.

Because of the newness of electron microscopy, the high cost of the instrument and the expertness required for proper maintenance, operation and interpretation, the electron microscope is certainly not now, nor is it likely to become soon, an office instrument. A beginning has been made, however, in application of electron microscopy to the differentiation of certain related viruses.<sup>20</sup> Such uses and the newly developing technics of preparing tissue sections will probably soon give electron microscopy areas of application in diagnostic laboratories in the larger hospitals and institutes. The prospect which is most exhilarating, however, is that of pure scientific research, the exploration of one, possibly two new orders of magnitude of fine dimensions by electron microscopy supplementing other current research instruments and technics.

On the grave of John Herschel in Westminster Abbey is the inscription:

"Joannes Herschel, Gulielmi Herschel natu, opere, fama. filius unicus,  
'coelis exploratis,' hic prope Newtonum requiescit.  
Generatio et generatio mirabilia dei narrabunt."

#### BIBLIOGRAPHY

1. ZWORYKIN, V. K., MORTON, G. A., RAMBERG, E. G., HILLIER, J., and VANCE, A. W.: *Electron optics and the electron microscope*, 1945, John Wiley and Sons, New York.
2. HILLIER, J.: Some remarks on the image contrast in electron microscopy and the two-component objective, *Jr. Bact.*, 1949, lvii, 313-317.

25. RAKE, G., BLANK, H., CORIELL, L. L., NAGLER, F. P. O., and SCOTT, T. F. McN.: The relationship of varicella and herpes zoster: electron microscope studies, Jr. Bact., 1948, lvi, 293-303.\*
26. NAGLER, F. P. O., and RAKE, G.: The use of the electron microscope in diagnosis of variola, vaccinia and varicella, Jr. Bact., 1948, lv, 45-51.
27. HAMRE, D., RAKE, H., and RAKE, G.: Morphological and other characteristics of the agent of feline pneumonitis grown in the allantoic cavity of the chick embryo, Jr. Exper. Med., 1947, lxxxvi, 1-6.
28. RAKE, G.: The initial body and the plaque form in the chlamydozoaceae, Jr. Bact., 1947, liv, 637-640.
29. KUROCHKIN, T. J., LIBBY, R. L., GAGNON, E., and COX, H. R.: Size and morphology of the elementary bodies of the psittacosis-lymphogranuloma group of viruses, Jr. Immunol., 1947, lv, 283-287.
30. RUSKA, H.: Morphologische Befunde bei der bacteriophagen Lyse, Arch. ges. Virusforschung, 1942, ii, 345-387.
31. KOTTMANN, U.: Morphologische Befunde aus taches vierges von Colikulturen, Arch. ges. Virusforschung, 1942, ii, 388-396.
32. LURIA, S. E., DELBRÜCK, M., and ANDERSON, T. F.: Electron microscopic studies of bacterial viruses, Jr. Bact., 1943, xlv, 57-77.
33. ANDERSON, T. F.: On a bacteriolytic substance associated with a purified virus, Jr. Cell. and Comp. Physiol., 1945, xxv, 1-15.
34. WYCKOFF, R. W. G.: Symmetrical patterns of bacteriophage production, Proc. Soc. Exper. Biol. and Med., 1947, lxvi, 42-44.
35. WYCKOFF, R. W. G.: The electron microscopy of developing bacteriophage. I. Plaques on solid media, Biochim. et Biophysica Acta, 1948, ii, 27-37.
36. SMILES, J., WELCH, F. V., and ELFord, W. J.: The influence of antibacterial substances on the interaction of bacteria and bacteriophages. 2. Optical studies of the penicillin effect, Jr. Gen. Microbiol., 1948, ii, 220-227.
37. HILLIER, J., MUDD, S., and SMITH, A. G.: Observations with improved electron microscopic techniques on the internal structure of *Escherichia coli* cells and the generation of coliphage, Sci. Proc. Am. Assoc. Path. and Bact., Am. Jr. Path., 1948, xxiv, 715-716.
38. WOLPERS, C.: Zur Feinstruktur der Erythrocytenmembran, Naturwissenschaften, 1941, xxix, 416-420.
39. SCHMITT, F. O., HALL, C. E., and JAKUS, M. A.: Electron microscope investigations of the structure of collagen, Jr. Cell. and Comp. Physiol., 1942, xx, 11-33.
40. RICHARDS, A. G., JR., STEINBACH, H. B., and ANDERSON, T. F.: Electron microscope studies of squid giant nerve axoplasm, Jr. Cell. and Comp. Physiol., 1943, xxi, 129-143.
41. SCHMITT, F. O., HALL, C. E., and JAKUS, M. A.: The ultrastructure of protoplasmic fibrils, Biol. Symp., 1943, x, 261-276.
42. SCHMITT, F. O.: Ultrastructure and the problem of cellular organization, The Harvey Lectures, 1945, xl, 249-268.
43. HALL, C. E., JAKUS, M. A., and SCHMITT, F. O.: An investigation of cross striations and myosin filaments in muscle, Biol. Bull., 1946, xc, 32-50.
44. SCHMITT, F. O., BEAR, R. S., HALL, C. E., and JAKUS, M. A.: Electron microscope and x-ray diffraction studies of muscle structure, Ann. New York Acad. Sci., 1947, xlvii, 799-812.
45. JAKUS, M. A., and HALL, C. E.: Studies of actin and myosin, Jr. Biol. Chem., 1947, clxvii, 705-714.
46. HAWN, C. VON Z., and PORTER, K. R.: The fine structure of clots formed from purified bovine fibrinogen and thrombin: a study with the electron microscope, Jr. Exper. Med., 1947, lxxxvi, 285-292.
47. GROSS, J., and SCHMITT, F. O.: The structure of human skin collagen as studied with the electron microscope, Jr. Exper. Med., 1948, lxxxviii, 555-568.

- nucleus in *Bacillus mycoides* grown in a nitrogen-free medium, Jr. Bact., 1947, liii, 539-553.
73. MUDD, S., and ANDERSON, T. F.: Demonstration by the electron microscope of the combination of antibodies with flagellar and somatic antigens, Jr. Immunol., 1941, xlii, 251-266.
  74. ANDERSON, T. F., and STANLEY, W. M.: A study by means of the electron microscope of the reaction between tobacco mosaic virus and its antiserum, Jr. Biol. Chem., 1941, cxxxix, 339-344.
  75. ARDENNE, M. v., FRIEDRICH-FREKSA, H., and SCHRAMM, G.: Elektronenmikroskopische Untersuchung der Präcipitinreaktion von Tabakmosaikvirus mit Kaninchenantiserum, Arch. ges. Virusforschung, 1941, ii, 80-86.
  76. MUDD, S., HEINMETS, F., and ANDERSON, T. F.: The pneumococcal capsular swelling reaction, studied with the aid of the electron microscope, Jr. Exper. Med., 1943, lxxviii, 327-332.
  77. MUDD, S., and ANDERSON, T. F.: Selective "staining" for electron micrography: The effects of heavy metals on individual bacterial cells, Jr. Exper. Med., 1942, lxxvi, 103-108.
  78. MORTON, H. E., and ANDERSON, T. F.: The morphology of *Leptospira icterohemorrhagiae* and *L. canicola* as revealed by the electron microscope, Jr. Bact., 1943, xlv, 143-146.
  79. JOHNSON, F. H.: Observations on the electron microscopy of *B. cereus* and tyrothricin action, Jr. Bact., 1944, xlvii, 551-557.
  80. SHANAHAN, A. J., EISENSTARK, A., and TANNER, F. W.: Morphology of *Escherichia coli* exposed to penicillin as observed with the electron microscope, Jr. Bact., 1947, liv, 183-189.
  81. WERNER, G. H., and KELLENBERGER, E.: Le rôle du microscope électronique dans l'étude du mode d'action des antibiotiques, Bull. Acad. Suisse des sci. méd., 1948, iv, 263-274.
  82. BABUDIERI, B.: L'azione antibatterica di alcuni antibiotici, studiata col microscopio elettronico, Rendiconti dell' istituto superiore di Sanita, Roma, 1948, xi, 577-598.
  83. FLEWETT, T. H.: Nuclear changes in *Bacillus anthracis* and their relation to variants, Jr. Gen. Microbiol., 1948, ii, 325-333.
  84. TATUM, E. L., and LEDERBERG, J.: Gene recombination in the bacterium *Escherichia coli*, Jr. Bact., 1947, liii, 673-684.
  85. LEDERBERG, J.: Gene recombination and linked segregations in *Escherichia coli*, Genetics, 1947, xxxii, 505-525.
  86. LEDERBERG, J.: Problems in microbial genetics, Heredity, 1948, ii, 145-198.
  87. LURIA, S. E.: Recent advances in bacterial genetics, Bact. Rev., 1947, xi, 1-40.
  88. DAWSON, I. M., and McFARLANE, A. S.: Structure of an animal virus, Nature, 1948, clxi, 464-466.
  89. ANDERSON, T. F.: Morphological and chemical relations in viruses and bacteriophages, Cold Spring Harbor Symposia on Quantitative Biology, 1946, xi, 1-13.
  90. COSSLETT, V. E.: Recent advances in electron microscopy in the United Kingdom, Research, 1948, i, 293-305.
  91. O'BRIEN, H. C., and MCKINLEY, G. M.: New microtome and sectioning method for electron microscopy, Science, 1943, xcvi, 455-456.
  92. FULLAM, E. F., and GESSLER, A. E.: A high speed microtome for the electron microscope, Rev. Sci. Instruments, 1946, xvii, 23-35.

pharmacologic and mechanical aspects of direct medication of the lung in man. Penicillin was chosen for this study for several reasons. It is, at present, the most frequently used agent in this form of therapy. It is free from serious toxic side reactions; it is not inactivated in the presence of pus; it is fairly stable in body fluids at freezing temperatures, and its assay in these fluids, although cumbersome, is readily accomplished by a trained bacteriologist.

The various factors requiring study are: (1) the pharmacodynamics of absorption and excretion following intratracheal and aerosol administration as contrasted to parenteral administration; (2) the action, if any, of various vehicles, other than saline, on absorption; (3) the effect of suppuration of the lung on the absorption mechanism; and lastly, (4) the relative efficiency of various methods of aerosolizing therapeutic agents. This report deals with the pharmacodynamics of absorption and excretion from the normal human lung.

Absorption from normal alveoli involves a more complex mechanism than absorption from muscle or subcutaneous tissue. Fluids must pass through the epithelium-lined wall of the alveoli and then cross the endothelium-lined capillaries into the blood stream. An alternative route is presented by the endothelium-lined lymphatics with which the alveoli are richly supplied. It is well known that fluids are absorbed from the bronchioles, bronchi and even the trachea. The relatively small surface area of the tracheobronchial tree as compared to that of the alveoli, makes absorption from the tracheobronchial mucosa quantitatively unimportant. As previously mentioned, the literature contains few references to the manner in which molecules of various sizes are absorbed from the lungs. The only studies recorded have been made in relation to war gas poisoning, pulmonary edema, and in Drinker's fundamental work on the lymphatic drainage of the lungs. Winternitz and Smith,<sup>6</sup> after the First World War, demonstrated that physiologic saline was rapidly absorbed when injected into the trachea of anesthetized dogs. Phenolsulfonphthalein, similarly administered, appeared almost immediately in the urine. Courtice and Phipps,<sup>7</sup> more recently in the course of studies with phosgene poisoning, administered water, physiologic saline and serum endotracheally to anesthetized rabbits and dogs and collected the flow from the right lymphatic duct in the latter. They were able to calculate the amount of fluid absorbed from the lungs by comparing the normal heart/lung weight ratio to that found after sacrificing the experimental animals at various intervals. Figure 1, taken from their article, illustrates their findings: 80 per cent of the water and 23 per cent of the saline were absorbed within the first hour. Serum absorbed very slowly, about four days being required for complete removal of all the material. The lymph flow was not appreciably increased above the normal; thus very little of this fluid was absorbed by the lymphatics. The ease with which water and molecules the size of sodium chloride and even phenolsulfonphthalein are absorbed from the lung is now evident. Drinker<sup>8</sup> in similarly arranged experiments,

A rational approach to the study of absorption and excretion of penicillin administered by the aerosol route necessitates an accurate determination of the amount of the active agent which actually reaches the pulmonary epithelium. It would seem, at first, that this amount might be calculated by comparing the total urinary excretion of the intramuscularly administered penicillin to that excreted following aerosol administration. If no penicillin were inactivated or detoxified within the body, such a comparison would hold. However, it is well established that only 40 to 60 per cent of parenterally administered penicillin can be recovered from the urine.<sup>10, 11, 12</sup> Moreover, the processes by which the balance of the biotherapeutic agent is detoxified or inactivated and the organs involved in this mechanism have not been established. Penicillin given intravenously to patients with complete renal shutdown disappears from the blood at a logarithmic rate with a half-life of about two hours.<sup>13</sup> Any interference with urinary excretion, due to renal insufficiency or drugs competing with penicillin for tubular excretion, such as diodrast, p-aminohippuric acid, caronamide, and others, may reduce the percentage of excreted penicillin in the urine to 30 per cent or less.<sup>12, 14, 15, 16</sup> Thus it appears that the amount of penicillin excreted is inversely related to the time of exposure within the body as a whole.

It also seems apparent that the capacity of the specific organ (the site of administration) to inactivate penicillin will inversely affect the urinary excretion. The influence of muscle or gastrointestinal mucosa on penicillin has been well established, but the effect which the pulmonary epithelium exerts is not known. It would, therefore, appear desirable to administer the drug into the tracheobronchial tree in such a fashion that no losses occur. If the percentage of urinary excretion under such conditions were known, a comparison with the excretion of aerosolized penicillin would be valid, and the effectiveness of this latter mode of administration could be calculated. Large losses with inhalational administration may be expected, largely due to technical difficulties. Loss in the apparatus and in the mouth can be relatively easily determined, as described elsewhere.<sup>17</sup> However, it is not so easy to determine the amount of active agent lost to the outside air. This loss may be expected to be the largest due to the following: (1) part of the inspired air (the dead space air) does not reach the alveoli and, therefore, most of the fluid particles are not removed; (2) the smallest droplets may enter the alveoli and leave them again on expiration without having been deposited; and (3) prevention of some loss to the outside air during aerosolization is impossible. A quantitative basis for the study of absorption and excretion following pulmonary administration requires a method by which the above mentioned losses are eliminated. We therefore elected to administer penicillin solution directly into the tracheobronchial tree by endotracheal catheter.

#### METHODS

The procedure used for endotracheal catheterization was identical to that used by the Thoracic Surgical Service to instill radio-opaque oil for

refrigerated for no longer than 24 hours. Storage for longer periods of time caused a loss in penicillin activity detectable by this method. Urines were not buffered since it has been shown that penicillin excreted in the urine is more stable than commercial penicillin and will tolerate a pH as low as 2.2 for long periods of time.<sup>23</sup> This method of assay is no more accurate than other methods of biological assay involving serial dilution. Each numerically expressed level signified that the specimen contains about half as much active substance as would be needed for a positive reaction in the next tube. In order not to give a false impression of accuracy, we have used the values of 0.16, 0.08, 0.04, 0.02, etc., rather than the values obtained by serially dividing 20 (the number of units per c.c. of standard) by 2, namely 10.... 2.5.... 0.625.... 0.156, 0.078, 0.039, 0.019.

### RESULTS

A total of 297 specimens were assayed, of which 167 were bloods, 108 urines and 22 apparatus and mouth rinses. Ten volunteers received 100,000 units of penicillin intramuscularly in 1 c.c. of saline (chart 1). The results

CHART I

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline (K-Salt) Penicillin (C.S.C.) in 1 c.c. Saline by the Intramuscular Route in 10 Subjects

	Blood							Urinary Excretion				
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.
No. 1	1.25	.63	.08	—	.02	—	—	24,960	5,070	—	390	27
No. 2	.16	.16	.08	—	—	—	—	—	—	—	—	—
No. 3	.31	.63	.31	.08	.04	.02	.00	4,368	10,250	13,750	2,340	300
No. 4	.63	.31	.08	.04	.00	.00	.00	72,500	10,750	4,750	796	900
No. 5	1.25	.63	.31	.08	.04	.00	.00	18,750	4,750	12,250	—	250
No. 6	2.50	1.25	.16	.08	.00	.00	.00	22,500	6,250	14,750	—	1,875
No. 7	1.25	.63	.23	.08	.02	—	—	17,750	3,750	4,368	725	204
No. 8	.63	.63	.16	.08	.02	.02	.00	31,500	12,000	2,934	897	31
No. 9	1.25	.63	.16	.04	.00	.00	.00	35,500	11,500	1,248	117	24
No. 10	1.25	.63	.31	.16	.04	.02	.00	35,250	19,375	4,992	702	689
Average	1.05	.61	.19	.07	.02	.01	.00	29,231	9,299	7,380	852	478
									(Total—47,240)			

varied somewhat from one individual to another but, on the whole, were fairly uniform. The highest blood levels occurred one-half hour after administration and the average level, at that time, was about 1 unit per c.c. of serum. A rapid decline followed and levels generally considered to be significant were maintained for three hours only. There was no evidence of any penicillin activity at the end of six hours in any of the blood specimens. The urinary excretion paralleled these blood levels very closely. An average of 29,231 units was excreted during the first hour with a rapid decline thereafter. The total average excretion, 47,240 units or 47.24 per cent, was slightly below the figure generally reported in the literature.



maintained for twice as long as with intramuscular administration (six hours). Urinary excretion correspondingly was much lower at one hour (8,060 units) and fell off less rapidly; almost an equal hourly amount was excreted from the second to the sixth hour. The total excretion of 15.9 per cent was roughly one third that obtained following intramuscular administration. These serum levels and urinary excretions are compared in figure 2.

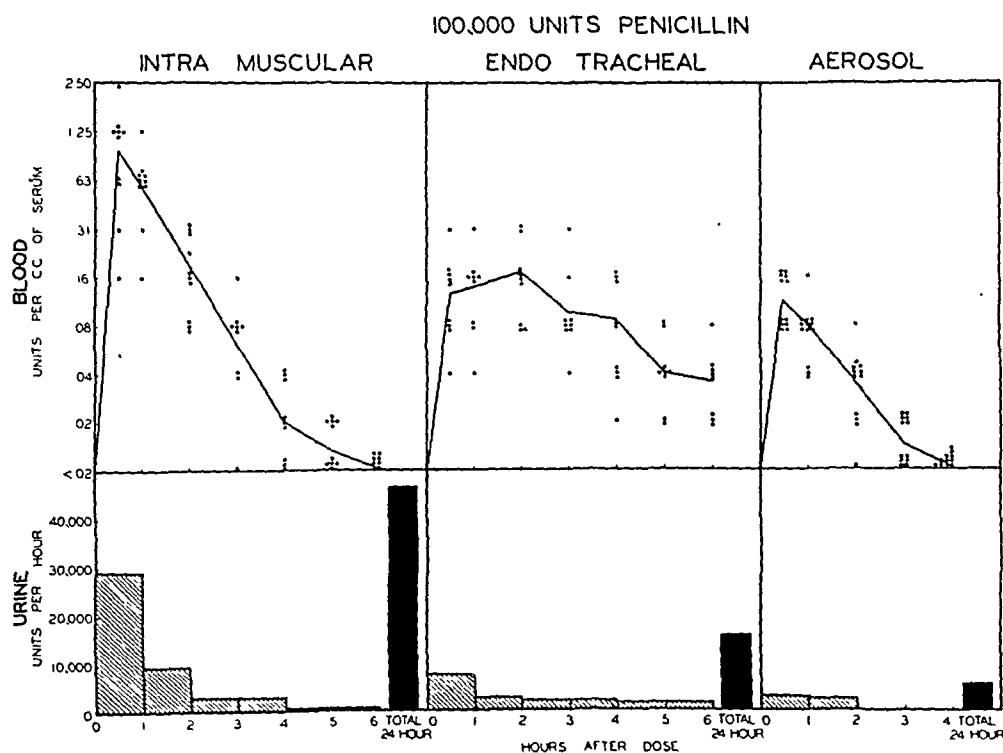


FIG. 2. Blood levels and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by various routes in normal male subjects.

Twelve patients received 100,000 units of penicillin in 1 c.c. of saline by aerosolization with the nebulizer-rebreathing bag apparatus (chart 3). The average blood level at one-half hour (0.12 unit per c.c.) parallels the corresponding level following endotracheal injection. Although the average at two hours was 0.04 unit per c.c., five of the 12 serums showed less than this therapeutically effective amount. No significant levels were encountered after two hours. Thus, although the aerosol curve reaches almost the same peak as the endotracheal curve, it drops off more quickly. Urinary excretion corresponds very closely. The total excretion averaged 5.46 per cent, approximately one third of the endotracheal excretion. These relationships are illustrated in figure 2.

### DISCUSSION

On comparing the parenteral and endotracheal blood level curves, several facts become evident. Absorption from the alveoli is much slower than from

blood levels by this route, injections are necessary only one-half as often as a similar dose given parenterally. Several methods of endobronchial administration of penicillin have been previously suggested. Kay and Meade<sup>27</sup> injected 250 to 10,000 units in 3.0 to 5.0 c.c. of saline by indirect laryngoscopy through a laryngeal cannula, without anesthesia, and reported favorable results in ulcerative tracheobronchitis, minimal bronchiectasis, and in preoperative treatment. Moore and Thompson<sup>28</sup> treated severe bronchiectasis with bronchial lavage and intratracheal penicillin and sulfathiazole under nupercaine anesthesia. Bobrowitz et al.<sup>29</sup> gave six bronchiectatic patients 50,000 to 250,000 units a day by the supraglottic method of instillation following cocaineization; they recorded rapid and satisfactory symptomatic improvement. Romansky<sup>30</sup> treated 12 cases of pulmonary suppurative disease with endotracheal penicillin suspended in iodized heavy oil.

We do not propose this form of treatment as a routine measure for several reasons. In order to obtain penicillin levels comparable to the ones we obtained, it is necessary to abolish the cough reflex by topical anesthesia. This not only introduces the well known hazards of topical anesthesia, but also violates an important therapeutic principle in the management of bronchopulmonary disease—maintenance of adequate cough reflex. This would be highly undesirable in the very diseases where primary application of penicillin to the tracheobronchial tree is indicated. Finally the technic of endotracheal intubation is more difficult and not as well tolerated by the patient as aerosolization.

In another study, dealing with absorption of penicillin in chronic suppurative pulmonary disease, we have consistently shown that parenterally administered penicillin does not reach the purulent sputum.<sup>31</sup> It has been the impression for some time that parenteral therapy will not penetrate the walled-off purulent cavity but will improve a surrounding pneumonitis.<sup>27, 28, 29</sup> Since the primary aim of penicillin administered directly to the lung is the production of high local concentrations, the nebulizer is the most practical tool by which the therapeutic agent can be placed at the site of the pathologic process. Endotracheal manipulation and topical anesthesia are not necessary. Most patients are easily taught to use the aerosol apparatus themselves in the hospital or at home. Furthermore, we have shown elsewhere that the amount of penicillin deposited in the lung, as evidenced by the penicillin excreted in the sputum, compares favorably with the endotracheal method. Our<sup>31</sup> experiences on the Inhalational Therapy Service and the Thoracic Surgical Service do suggest, however, that in certain special cases biotherapeutic agents may be given to great advantage by the endotracheal route. Such is the case when endotracheal intubation is necessary, primarily for other reasons, as at time of bronchoscopy or bronchography, during the course of endotracheal aspiration therapy following thoracic surgery, or in the treatment of acute atelectasis. Our experiences also suggest that when a rapid and striking reduction of sputum is necessary prior to surgery for sup-

solution is actually absorbed by the lungs, one sixth is lost within the apparatus and the oropharynx and almost one-half is lost into the air.

### SUMMARY

1. Intratracheal administration of penicillin in saline solution in normal, anesthetized volunteers revealed that the penicillin molecule is readily absorbed into the blood stream from the alveoli. This absorption is notably slower than that following parenteral administration.

2. Blood levels following intratracheal instillation do not reach the early high peaks seen on intramuscular administration but therapeutically significant blood levels are maintained for twice as long a period of time. The average urinary excretion is 15.9 per cent, or about one third of that following parenteral administration. This suggests that the lung may act as a *depot* from which penicillin may be slowly released.

3. Intratracheal administration is suggested as a practical and advantageous method of therapy under certain, special circumstances.

4. Aerosolized penicillin solution results in early blood levels nearly as high as those obtained by endotracheal administration, but therapeutic levels are maintained for only one third as long a period of time.

5. Following aerosolization, 5.5 per cent of the administered penicillin is excreted into the urine; 10.2 per cent is lost within the apparatus, 8 per cent is lost in the oropharynx and 47.5 per cent is lost on expiration and other losses into the air. Thus one third of the aerosolized penicillin solution actually reaches the lung.

### BIBLIOGRAPHY

1. GRAESER, J. B., and ROWE, A. H.: Inhalation of epinephrine for the relief of asthmatic symptoms, *Jr. Allergy*, 1935, vi, 415-420.
2. BRYSON, V., SANSOME, E., and LASKIN, S.: Aerosolization of penicillin solutions, *Science*, 1944, c, 33-35.
3. BARACH, A. L., SILBERSTEIN, F. H., OPPENHEIMER, E. T., HUNTER, T., and SOROKA, M.: Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis and lung abscess: preliminary report, *Ann. Int. Med.*, 1945, xxii, 485.
4. SEGAL, M. S., and RYDER, C. M.: Penicillin aerosolization in the treatment of serious respiratory infections. A preliminary report, *New England Jr. Med.*, 1945, ccxxxiii, 747.
5. RICHARDS, D. W., BARACH, A. L., and CROMWELL, H. A.: Use of vaporized bronchodilator solutions in asthma and emphysema. A continuous inhalation method for severe asthmatic states, *Am. Jr. Med. Sci.*, 1940, cxcix, 225-232.
6. WINTERNITZ, M. C., and SMITH, G. H.: Preliminary studies in intratracheal therapy, collected studies on the pathology of war gas poisoning, 1920, Yale University Press, New Haven.
7. COURTICE, F. C., and PHIPPS, P. J.: The absorption of fluids from the lungs, *Jr. Physiol.*, 1946, cv, 186-190.
8. DRINKER, C. K., and HARDENBERGH, E.: Absorption from the pulmonary alveoli, *Jr. Exper. Med.*, 1947, lxxvi, 7-18.
9. RAWSON, R. A.: The binding of T-1824 and structurally related diazo dyes by the plasma proteins, *Am. Jr. Physiol.*, 1943, cxxxviii, 708-717.

# THE HEREDITY OF GOUT AND ITS RELATIONSHIP TO FAMILIAL HYPERURICEMIA \*

By ROBERT M. STECHER, M.D., F.A.C.P., A. H. HERSH, Ph.D., and  
WALTER M. SOLOMON, M.D., F.A.C.P., *Cleveland, Ohio*

DESPITE the fact that gout has long been recognized as a hereditary disease and that much study has been devoted to this phase of the problem, the exact pattern of inheritance has not been clearly identified. It seemed likely that a broader concept of the disease and the application of modern methods of genetic investigation to readily available data might add much to our understanding of the disease. The present study was undertaken in the hope that these potentialities might be realized.

The most striking features of gout have always been associated with the joint phenomena. Characteristically these consist of a series of sudden, acute, painful attacks of arthritis involving with decreasing frequency the joints of a big toe, the feet, the knees and the hands. The joints may become affected overnight and are greatly swollen, very red, markedly tender and hot. There is often fever and leukocytosis. The attacks subside spontaneously in days to months and complete recovery is the rule. Only as a result of repeated attacks and after many years does chronic joint damage with deformity occur. The deposition of uric acid crystals as tophi in the skin about the ears, or in bones about the joints and resulting in punched-out areas seen by roentgen-ray, are the pathognomonic lesions of the disease. They appear only late in the disease, if at all, and they escape detection entirely in many victims. Because the joint manifestations of gout characteristically occur only in middle or later life and because they are often atypical and cannot be correctly identified, many affected members of the gouty family are not recognized and the genetic pattern is rarely complete.

Gouty patients have an abnormally high level of uric acid in the blood, one manifestation of the faulty uric acid metabolism which is characteristic of the disease. Hyperuricemia is present whether the patient is having gouty attacks or not and this abnormality has been observed in patients before they developed clinical gout. A substantial proportion of the near relatives of gouty people have been found to have hyperuricemia. This suggested that the genetic pattern and the mechanism of inheritance of familial hyperuricemia might be recognized and that analysis of this trait could yield valuable information about the heredity of gout. The present study, therefore, is one of the genetics of familial hyperuricemia and for this purpose familial hyperuricemia is considered to have exactly the same significance as clinical gout.

\* Received for publication April 21, 1947.

From the Department of Medicine, School of Medicine at City Hospital and the Department of Biology, Western Reserve University.

TABLE I  
Serum Uric Acids  
1272 determinations on 1,162 individuals

	Number of Individuals	Number of Determinations	Determinations below 6.5 mg.	Determinations 6.5 mg. or over	Average
A. Gouty families					
1. Index cases	41	77	3	74	8.12
2. Hyperuricemia	17	23	1	22	7.37
3. Normal relatives	120	124	123	1	
4. Spouses of gout	23	24	22	2	
Total	201	248	149	99	
B. General population					
5. Normal kidney function	878	927	893	34	
6. Nitrogen retention	83	97	72	25	
Total	961	1,024	965	59	
Grand total	1,162	1,272	1,114	158	

stances, 94 per cent of 177 determinations on 21 gouty subjects being over 7 mg. per 100 c.c. Among 100 non-gouty subjects there were only three determinations above 6 mg.

Because of the importance of recognizing a definite level between hyperuricemia and normal it seemed desirable to determine the dividing line to be used in this study from our own experience of 1,272 tests. These included 248 tests on 41 gouty patients and 159 of their relatives or spouses and 1,024 tests done routinely on 961 patients on the medical wards of Cleveland City Hospital, shown in table 1. All determinations used in this study were made by one individual using Benedict's direct method, and read with a Klett Electric Colorimeter on serum separated from clotted blood. Specimens were collected under oil without regard to fasting.

Table 2 shows the distribution of values in various classes of individuals. Examination of this table shows a natural division of high and low levels

TABLE II  
Serum Uric Acid Levels  
Distribution of 1,272 determinations

	0- 1.9	2.0- 2.4	2.5- 2.9	3.0- 3.4	3.5- 3.9	4.0- 4.4	4.5- 4.9	5.0- 5.4	5.5- 5.9	6.0- 6.4	6.5- 6.9	7.0- 7.4	7.5- 7.9	8.0- 8.4	8.5- 8.9	9+
A. Gouty families																
1. Index cases									1	2	8	13	14	12	15	12
2. Hyperuricemia									1	1	7	7	3	3		2
3. Normal relatives			6	11	21	22	16	25	18	4	1	1				
4. Spouses of gout		1	3	2	2	3	6	2	2	1	1		1			
Total 248		1	9	13	23	25	22	27	21	8	17	20	18	15	15	14
B. General population																
5. Normal kidney function	54	65	106	136	153	162	80	70	42	25	12	5	8	1	2	6
6. Nitrogen retention	2	1	5	7	11	11	12	6	11	6	4	7	3	2	3	6
Total 1,024	56	66	111	143	164	173	92	76	53	31	16	12	11	3	5	12
Grand total 1,272	56	67	120	156	187	198	114	103	74	39	33	32	29	18	20	26

TABLE III  
Pedigrees of 40 Gouty Families

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
1. M. A. male (63) 8.0 8.0		(62) 2.9				(39) 4.4 (38) 5.4 (35) 5.9 (31) 5.9 (27) 4.9 (23) 5.1	(40) 3.9
2. C. B. male (65) 10.8 9.5				(70) 5.2			
3. J. B. male (50) 6.5			(72) 4.2		(41) 2.6		
4. G. C. male (62) 7.8 7.2 7.8 7.3		(58) 5.6				(36) 5.2	(28) 4.6
5. E. C. male (61) 7.6 8.1					(64) 3.7 (62) 4.3 (60) 3.7 (56) 5.1		(38) 5.1
6. D. D. male (70) 8.4 8.8						(48) 4.1 (38) 4.6 (32) 5.8 (25) 7.2	(36) 5.4
7. L. D. male (48) 7.3				(66) 5.4	(51) 7.1		
	8. B. B. female (51) 7.1	(45) 6.0				(12) 4.8	(30) 3.7 (28) 4.8 (26) 4.1 (25) 4.7 (24) 4.5 (22) 4.8 (19) 4.8 (16) 4.3
9. F. D. male (46) 7.0 5.5			(74) 4.4				

TABLE III—*Continued*

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
21. O. K. male (53) 8.9	•	(55) 4.6		(61) 6.1		(14) 4.0	(32) 4.4
22. E. L. male (50) 9.2		(48) 5.2	(81) 4.8	(52) 5.3		(19) 5.7	(17) 4.9
23. A. L. male (62) 8.5 9.2 8.5				(48) 7.5			
24. O. L. male (68) 7.2 8.1		(66) 3.3					(39) 3.0 (34) 3.6
25. S. N. male (43) 6.6 6.3		(40) 2.9	(65) 4.5	(37) 5.6			(13) 4.4
26. J. P. male (58) 7.3 8.4 8.7 10.7			(80) 9.4 8.3	(55) 3.4 (44) 3.4	(49) 3.9 (42) 2.8		
27. J. P. male (66) 7.7 7.2 9.0 7.6				(70) 6.1 (65) 5.6		(42) 5.5 (35) 5.8	(41) 3.7
28. E. S. male (46) 8.5		(44) 4.8	(69) 9.3	(45) 7.0		(19) 5.7	(16) 4.7
	29. Mrs. S. female (69) 6.7 9.3				(71) 6.9 (65) 7.1		
	30. Mrs. B. female (65) 7.1	(80) 4.5				(45) 7.6 (40) 8.1 (38) 5.2	
	31. Mrs. B. female (71) 6.9						(48) 5.3 (31) 5.2

presented in table 3. This shows the age when seen and sex of each index case, the age, sex and relationships of each relative examined and all of the serum uric acid determinations done on the entire group in the course of this study. The spouses are included so that the reader may reconstruct the pedigrees if he wishes. Each secondary index case is a duplication having been shown before in a previous family. Initials are given only for index cases. The relationship is shown by the column, age is given in brackets. The relatives we have considered affected are indicated by underlining.

Of the 44 primary index cases, all had gout, all were male, all had high serum uric acid levels, save three men with undoubted gout, known to have had a high level of whole blood uric acid but who died before this study was started, and whose families were known and available to us. Seventy-seven serum uric acid determinations on these 41 index cases averaged 8.12 mg. per cent. The lowest determinations were 5.5, 6.2 and 6.3 mg. per cent, these three being all that fell below 6.5 mg. each in an individual who had other determinations above this level.

TABLE IV  
Hyperuricemia in Relatives

	Mother	Brother	Sister	Son	Daughter
Number examined	11	23	24	33	45
Number affected	2	4	5	5	0
Proportion affected (%)	18	17	21	15	0

Having the above data available, it seemed desirable to investigate the proportions of involvement among different degrees of relationship. The results are shown in table 4. Because of the known preponderance of gout in males it seems desirable to consider each sex separately. Inquiry was made concerning all the parents. Of 88 parents of 44 primary index cases only 12 were available for examination. These included the mother in 11 families. Twice she was found to have hyperuricemia but never gout. One father (of the index case J. H., family No. 15) examined was thought to have gout clinically but he showed a normal uric acid level twice. One other father was reported to have had gout but he has not been included in our computations. Thus 2 of 12 parents or about 17 per cent of those examined were found to have hyperuricemia. No attempt was made to analyze involvement of parents of the hyperuricemic relatives because they had one involved parent by definition.

Of the primary index cases, 16 had brothers. These 16 men had 23 brothers of whom 4 or 17 per cent had hyperuricemia. Twelve primary index cases had 22 sisters. One other person, the mother of an index case, had hyperuricemia and her 2 sisters had hyperuricemia, one of them gout. Of 24 sisters then, 5 or 21 per cent had hyperuricemia. The incidence of hyperuricemia in the siblings of gouty people is about 20 per cent and there is no significant sex difference.



times. Seventeen of the fathers had gout, two had hyperuricemia. All the mothers had hyperuricemia.

Study of table 5 shows the proportion of involved offspring from various combinations of involved and normal parents. In only one family, No. 15, were both parents involved, the father with gout, the mother with hyperuricemia. The four daughters from this union were normal. There were no sons. In nine families sons were born of gouty fathers and normal mothers (Nos. 38, 1, 14, 18, 4, 21, 22, 28, 17). In two other families the father had hyperuricemia without gout, the mother was normal (Nos. 32, 33). These families had 18 sons and 16 daughters. In only one family of this known combination was an affected son produced (No. 38). In five other families with gouty fathers, but mothers unknown (Nos. 6, 27, 10, 37, and 40), there were nine sons and two daughters with only one son affected (No. 6). There were six families with mothers with hyperuricemia and three normal fathers (Nos. 8, 30, 13) and three fathers untested (Nos. 28, 26, 31). In family 26 reference is to parents of the index case. There were 11 sons in these families of whom six were affected. Four of these families had daughters (Nos. 8, 26, 13, 31), a total of 13, all normal. Both parents of index case No. 15 were normal and both sons, their only children, were affected. In eight other families, the mothers were normal and fathers unknown (Nos. 39, 3, 9, 10, 11, 19, 22, and 25). These eight families will not be discussed because the possibilities of an affected father cannot be excluded.

In six families with gouty fathers (Nos. 34, 24, 20, 36, 25, 5) and another family with hyperuricemic father (No. 16) and the mothers normal or unknown, there was a total of 13 daughters, all normal, but no sons.

It is seen that in every instance where something was known about at least one parent, not a single affected daughter among 48 was found although there were 10 affected of 40 sons. Furthermore, the degree of involvement in the parents was no reliable index as to how they would transmit the abnormality. Two affected parents had only four daughters, all unaffected. Two normal parents with only two sons had both affected. Of 23 families with the father involved but mother normal or unknown there was a total of 27 sons, of whom only one each in two different families was affected. There were 31 daughters in these families, only three of whom were in the two families with affected sons. There were six families with affected mothers and normal or unknown fathers. These families produced 11 sons of whom six were affected. Four of these six families produced affected sons. These four families with six affected sons produced only three daughters. Thus with the father affected, only two of 27, or 8 per cent of the sons were affected. With mothers affected, six of 11, or one-half of the sons were affected. The effect of sex was marked. The apparent immunity of daughters is not so convincing when we realize that only 6 of 21 families having sons and with one parent involved proved that they could transmit hyperuricemia to a son. Six daughters only sprang from these six

TABLE VI—*Continued*

Family	Total Sons	Affected Sons	Total Daughters	Affected Daughters	Fathers	Mothers
Sibships with Affected Sisters						
29	0	0	3	3	Unknown	Unknown
10*	1	1	1	1	Unknown	Unknown
12*	1	1	1	1	Unknown	Unknown
7*	2	1	1	1	Unknown	Unknown
Sibships with Unaffected Sisters Only						
15			4	0	Gout	H.U.A.
34			4	0	Gout	Normal
24			2	0	Gout	Normal
16			2	0	H.U.A.	Normal
36			1	0	Gout	Normal
25			1	0	Gout	Normal
5			1	0	Gout	Unknown
31			2	0	H.U.A.	Unknown

\* Shown in table of Affected Sons.

is known of the parents. According to table 5, there were 24 sibships with at least one affected brother. In eight of these the constitution of one or both parents is known. These 24 sibships had 51 males of whom 29 or 57 per cent were affected. Of the 24 families 15 or 62 per cent had daughters, 26 in number, of whom one each in three sibships was affected (Nos. 10, 12, 7). Another 15 sibships had 23 males, all normal. Each of these families had an affected parent or it would not have been included in the study. Ten of the sibships had 23 females, all normal. Four families had affected sisters, three mentioned above (Nos. 10, 12, 7) and another (29) with three sisters all involved. Eight additional sibships without sons had 17 daughters, all normal.

Involvement of women with hyperuricemia was rare but significant. Of the four sibships with involved women, a total of six women were examined and all found involved. Of four brothers of these women, three were found affected. Nine of the 10 people in these four sibships involving affected women were affected. Only two other affected females were discovered in the entire study, a spouse (No. 15) and a mother (No. 26). Of the eight women with hyperuricemia, only one could possibly be considered to have clinical gout.

Consideration of the data of table 3 and table 5 is sufficient to show that the inheritance of hyperuricemia exhibits certain irregularities. This is emphasized more clearly by an examination of the pedigrees of several of the more significant families. Figure 1 shows in pedigree form the data for families 15 and 16, while figure 2 gives the pedigree for the related families 28, 29, 30, 31, 32 and 33 of table 3.

parents with affected offspring were heterozygous for a dominant gene which acts irregularly in many families. It is clear that a dominant gene which lacks penetrance can resemble a recessive in some pedigrees.

These two pedigrees, taken in conjunction with the other families of table 3, justify the conclusion that the genetic peculiarities of hyperuricemia are mainly the expression of an autosomal dominant gene which lacks penetrance in both sexes, but with a much lower penetrance in the female than in the male, perhaps about one-seventh as much.

Gout is a disease in which the average age of recognition is in the middle or later life and the lack of penetrance observed might be dependent upon the low age of the population studied. The relationship of age to serum uric acid level was tested by computing the coefficient of correlation ( $r$ ). The determination was made for each sex separately. The value of  $r$  with its standard error was found to be  $+0.088 \pm 0.129$  for male relatives of gouty people. This shows complete lack of correlation indicating that there is no significant increase of the serum uric acid in males after the age of 20. No alteration in penetrance is to be expected with advancing years. The finding in regard to women is quite different. Here  $r$  was found to be  $+0.44 \pm 0.09$ , a degree of correlation which is definitely significant. A marked difference is thus revealed between men and women. Inspection of the correlation table shows that every woman with hyperuricemia was over 50 years of age, a fact which suggests that normal menstrual function inhibits the development of idiopathic hyperuricemia.

Whether the level of serum uric acid is definitely established for men at adolescence or earlier in childhood is at present unknown. The present series included only eight males below the age of 20, so that our observation on this point is limited. Talbott, however, observed hyperuricemia in four males under the age of 20, the youngest being 14. His observations differed from ours also regarding the age of females. Among the relatives of gouty patients, he records seven hyperuricemic women all under the age of 42, the youngest being 21.

From the above considerations we tentatively conclude that hyperuricemia is an autosomal dominant with low penetrance in both sexes, but considerably lower in the female than in the male. Since it is desirable wherever possible to put the conclusion to the numerical test, even when the data for making such a test may be somewhat inadequate and inconclusive, we have assembled the pertinent data from table 3 in table 7. It is well known that in analyzing human genetic data a correction must be made for small family size. When families are small, certain families of the proper genetic constitution but having several unaffected offspring will go unrecognized and therefore uncouned. The observed affected offspring will consequently be more than the theoretically expected number.

Hogben<sup>6</sup> has published tables of corrective factors for families of different size. These tables are for testing ratios in fraternities for genes with

With mothers affected all sons become involved. Fathers do not transmit to their sons. This situation is approached in this series in that six of eight sons of five affected mothers had gout. Fathers, however, do not transmit sex-linked characters to their sons but only produce carriers of their daughters. In this series three fathers transmitted gout to their sons, table 3, Nos. 7, 14, 38. Smyth and Freyberg<sup>6</sup> described two similar instances. The data do not support the theory that gout or hyperuricemia are sex-linked characters.

The possibility that hyperuricemia might be a recessive trait was tested in the following way: When one parent shows a trait and some of the children are affected, the other parent may be normal if the trait is dominant. If the trait be recessive, however, the phenotypically normal parent must be heterozygous or affected children will not appear. It is obvious that there must be a sufficient reservoir of heterozygotes in the population to give a reasonable probability that the required number of matings may occur with random mating. In other words the genetic analysis of the data of the pedigrees must be consistent with the gene frequencies in the population.

Since about one-eighth of the relatives of gouty people were found to have unsuspected hyperuricemia it seemed reasonable to suppose that this trait might be observed in a discoverable proportion of the general population selected at random. In an effort to test this supposition, routine serum uric acids were done on patients on the medical wards at City Hospital, care being taken only to exclude known gout. Of 1,024 determinations on 961 patients, only 59 or 5.7 per cent were over 6.4 mg. per 100 c.c. Those included 25 tests on patients with urea nitrogen retention, 16 with cardiac failure, eight malignant growths or leukemia, two pneumonia, four anemia or recent hemorrhage, and three, all below 6.8 mg., who subsequently had lower values and were considered normal. Only one patient, a diabetic, had a level of 9.1 mg. per 100 c.c., the only one of 961 individuals tested who might be considered to have constitutional hyperuricemia. This result was sufficient to discourage further attempts to discover the true incidence of constitutional hyperuricemia in the general population by this method.

Despite the obvious inadequacy of these data they were used tentatively as a basis for gene frequency analysis. Instead of using 1 in 1,000 for the proportion of hyperuricemia in the general population this figure was arbitrarily adjusted to 3 in 1,000 in order to be conservative in the conclusions. This assumption weights the argument strongly in favor of the theory that hyperuricemia is inherited as a recessive. Despite this advantage the theory earns little support in the following argument.

With hereditary characters the frequencies of homozygous dominants, heterozygotes, and homozygous recessives in a population mating at random agree with the equation  $d^2 + 2dr + r^2 = 1$ , where  $d$  (the frequency of the dominant gene) +  $r$  (the frequency of the recessive allele) = 1. If the incidence in the population is assumed to be 3 per 1,000, and the gene for the trait is dominant,  $d = 0.0017$ ,  $r = 0.9983$  and the corresponding frequencies

tion to high uric acid concentrates in the blood. These factors still remain unidentified despite intensive investigation for many years.

### SUMMARY

This study is based on 248 serum uric acid determinations on the 201 members of 44 gouty families as well as 1,024 serum uric acids on 961 patients examined routinely at City Hospital. A clear-cut division between hyperuricemia and normal was recognized clinically at 6.5 mg. per 100 c.c., which was confirmed by statistical analysis. The incidence of hyperuricemia in the relatives of gouty patients was found to be 18 per cent among 11 mothers, 17 per cent among 24 brothers, 21 per cent among 24 sisters and 15 per cent among 33 sons. Not a single daughter among 45 tested was found to have hyperuricemia.

There was no correlation between age and hyperuricemia among male relatives of gouty patients, but a significant correlation was found among female relatives. Since no female relative in this series was affected below the age of 50, it seems possible that normal menstrual function inhibits hyperuricemia.

On the assumption that gout and the hyperuricemia found in some of the relatives of gouty patients are the expression of the same genotype both in the same family and in different families, this series was developed in an attempt to detect the genetic mechanism involved. The genetic peculiarities of hyperuricemia are such that in some families it resembles an autosomal recessive, whereas in others it is more like an autosomal dominant. These peculiarities are, however, quite satisfactorily explained if the gene involved is an autosomal dominant which lacks penetrance in both sexes, but has a much lower penetrance in the female than in the male. A tentative estimate of the penetrance is about 84 per cent in the heterozygous male, about 12 per cent or less in the female. This conclusion brings the data of the pedigrees in good agreement with a tentative estimate of the gene frequencies in the general population.

*Note:* Since this article was submitted for publication, three studies have appeared which are pertinent to the subject: SMYTH, C. J., COTTERMAN, C. W., and FREYBERG, R. H., JR.: The genetics of gout and hyperuricemia—an analysis of 19 families, *Jr. Clin. Invest.*, 1948, xxvii, 749-759; SMYTH, C. J., STECHER, R. M., and WOLFSON, W. Q.: Genetic and endocrine determinants of the plasma urate level, *Science*, 1948, cviii, 514-515; HELLMAN, L.: Production of acute gouty arthritis by adrenocorticotropin, *Science*, 1949, cix, 280-281.

### BIBLIOGRAPHY

1. MCCracken, J. P., OWEN, P. S., and PRATT, J. H.: Gout: still a forgotten disease, *Jr. Am. Med. Assoc.*, 1946, cxxxii, 367-372.
2. BROCHNER-MORTENSEN, K.: One hundred gouty patients, *Acta med. Scandinav.*, 1941, cvi, 81-107.
3. FOLIN, O., and DAVIS, W.: The diagnostic value of uric acid determinations in blood, *Arch. Int. Med.*, 1915, xvi, 33-37.

# THE USE OF CURARE (D-TUBOCURARINE IN OIL AND WAX) IN THE TREATMENT OF MUSCLE SPASM IN RHEUMATIC DISORDERS \*

By H. M. MARGOLIS, M.D., F.A.C.P., and PAUL S. CAPLAN, M.D.,  
*Pittsburgh, Pennsylvania*

THE present report records our preliminary observations in a consecutive series of 58 cases of various types of rheumatic disease in which treatment with curare in oil and wax was instituted. Curare was administered in 51 cases in which muscle spasm actually existed. The remaining seven cases were those in which a diagnosis of psychogenic rheumatism was made. In these, subjective symptoms of "muscle stiffness" without objectively demonstrable spasm were prominent along with many other bizarre musculoskeletal symptoms. Curare was used in this group primarily for control purposes, as an aid in evaluation of results in the larger group. Although the number of patients studied is not large, the results have been definitive. The conclusions to be drawn with regard to the effectiveness of the drug in the various syndromes studied are unmistakable. This preliminary report may indicate not only the area of usefulness of the drug, as revealed by our experience, but may encourage further interest in its study in other, related types of rheumatic disease.

The historical background of the use of curare, the pharmacologic properties of which were first demonstrated by Claude Bernard as far back as 1850, and its physiologic properties, as well as its more recent applications have been well described in a series of publications by Schlesinger and Ragan.<sup>1, 2, 3, 4, 5</sup>

Briefly, tubocurarine is a quaternary ammonium salt. These salts, as a group, possess the property of paralyzing conduction at the myoneural junction. In certain concentrations, tubocurarine has an almost pure myoneural junction effect. This neuromuscular block can be employed therapeutically, because with certain specific concentrations of curare as employed in the present study, involuntary muscle spasm is abolished, whereas voluntary muscular contraction is entirely unaffected.

The effect of curare in creating myoneural block has been known for many years. Practical application of this knowledge was not possible, however, until recently, when a crystalline derivative of the crude alkaloid, with predictable pharmacologic properties and toxicity became available. The earlier aqueous preparations of curare were not well suited to the treatment

\* Received for publication May 18, 1948.

From the Department of Medicine and the Arthritis Services of The Montefiore and St. Margaret Memorial Hospitals and The John C. Oliver Memorial Research Foundation of The St. Margaret Memorial Hospital.

The results were recorded as either definitely beneficial; not beneficial; questionably beneficial.

Results were tabulated as definitely beneficial only when striking relief of symptoms occurred with curarization (estimated at an average of 85 per cent). These findings were confirmed by objective examination.

Results were tabulated as questionable when the patient reported slight subjective improvement which could not be confirmed by objective examination. In many instances it was felt that subjective change could not be directly attributed to curarization.

### ANALYSIS OF RESULTS

*Rheumatoid Arthritis.* There were 23 cases of generalized rheumatoid arthritis. The duration of the disease varied from one to 20 years, the majority of the patients (16 cases) having been ill for over five years. All presented typical clinical and roentgenographic evidence of rheumatoid arthritis; all were in a stage of activity as indicated clinically and by rapid sedimentation rates, and many of them showed characteristic deformities. These patients received three to six injections of 175 units (1.0 c.c.) of curare in wax and peanut oil every two to three days; this treatment was continued with one patient for a period of six weeks. In several instances reactions without relief of muscle spasm were noted following injection. In these cases administration of the drug was discontinued.

In none of these patients was there clinical evidence of definite improvement, either subjective or objective. In five cases there was questionable subjective improvement which could not be confirmed by examination. It is perhaps significant that of these five, one was suffering from Marie-Strumpell (rheumatoid) spondylitis and four presented evidence of Marie-Strumpell spondylitis associated with rheumatoid arthritis of peripheral joints. Three cases of typical rheumatoid spondylitis, however, were not benefited either subjectively or objectively.

*Periarthritis of Shoulder.* There were five cases of periarthritis of the shoulder. The roentgenograms in all were normal.

These patients presented the characteristic symptoms of pain in the shoulder and along the course of the deltoid muscle, pain always increased by attempts at abduction, external or internal rotation of the arm. In all cases normal range of motion was to some degree restricted. Definite adhesive changes limiting the range of mobility were associated in two. In these, manipulation of the shoulder under anesthesia was performed. In the other three cases restriction in the range of motion was caused entirely by muscle spasm. In one of these, manipulation of the shoulder was performed in the course of tonsillectomy, but no adhesions were present.

In all five cases of periarthritis of the shoulder there was distinct improvement, both subjectively and objectively, attributable to the administration of curare. In the two cases in which manipulation was performed to break

*Osteoarthritis with Associated Periarticular (Capsular) Fibrositis.* Six patients with clinical and roentgenographic evidence of osteoarthritis of peripheral joints with associated periarticular (capsular) fibrositis of either degenerative or perhaps infectious origin were treated.

In two of these patients questionable subjective improvement resulted from the administration of curare. Both were elderly. In both the onset of the fibrositic symptoms followed an acute respiratory infection; the sedimentation rates were accelerated. The findings indicated a capsulitis of apparently infectious origin, superimposed upon marked generalized osteoarthritis. Although these patients reported some alleviation of morning stiffness, the effect was negligible and probably attributable to the general therapeutic measures; rest, analgesics, and physiotherapy used concomitantly with curare.

Four of these patients presented osteoarthritis of the peripheral joints with symptoms indicative of an associated capsulitis of degenerative origin. They all had normal sedimentation rates. In none of these was there evidence of improvement, either objective or subjective, after repeated administration of curare in oil and wax.

*Fibromyositis.* Four patients with fibromyositis failed to derive any benefit from repeated administration of curare. One of these patients suffered from a generalized fibromyositis following an acute upper respiratory infection. The second patient manifested characteristic fibromyositic symptoms involving the shoulders, hips, and lower back. The fibromyositis in the third and fourth patients was localized to the cervical region.

*Psychogenic Rheumatism.* Seven patients presented the typical syndrome of psychogenic rheumatism in which a feeling of stiffness, muscle aching, and other types of pain, often bizarre, were associated with other psychoneurotic personality traits. A diagnosis of psychogenic rheumatism had previously been established both by direct examination as well as by exclusion of organic musculoskeletal disease. There was no hope of obtaining any therapeutic benefit in this group; they served as a control. In none of these cases was any improvement noted. Two patients described some degree of subjective improvement, but this, however, did not correspond to the usual description of the effect of curare. Subsequent injections of curare were said to have been of no benefit or to have been followed by actual increased severity of symptoms.

## DISCUSSION OF RESULTS

The beneficial effects of curare are always evidenced by prompt, dramatic relief of muscle spasm, generally after the first injection of the drug. Hence, long periods of trial are unnecessary. The specific physiologic effect of the drug is so clear cut that when beneficial therapeutic results are forthcoming, they should be evident to some degree after the very first injection. Except in the case of patients with psychogenic rheumatism, the response is generally



ployed in conjunction with physiotherapy and manipulative exercises. By overcoming muscle spasm, it may be possible in some of these instances to restore the full range of motion in the shoulder by physiotherapeutic measures, including exercise, when manipulative therapy under anesthesia might otherwise be required. The use of curare is also strikingly beneficial in conjunction with physiotherapeutic measures which we institute promptly after the breaking up of adhesions under anesthesia. In such cases we have found that the therapeutic exercises following manipulation were carried out more easily, with less discomfort, and with a better ultimate result, attained in a much shorter period of time. The number of cases so treated is small, however, so that final evaluation is not possible at this time.

The beneficial results of curare in the relief of low back pain demonstrates the specific value of this drug in the abolition of reflex muscle spasm. Curare should find its greatest field of usefulness in the treatment of low back pain when there is muscle spasm of reflex origin. Our two patients with low back pain (without sciatic radiation) who were not benefited from curare presented associated factors, especially an unfavorable psychogenic component which militated against a favorable result. Their evidence should therefore not detract from the otherwise consistently favorable results in this group of cases.

We found curare to be of no value in low back pain with sciatic radiation caused by nerve root irritation or pressure. These results confirm the observations of Schlesinger and Ragan<sup>4</sup> who also noted that with removal of the splinting action of muscle spasm, sciatic pain resulting from direct nerve root involvement was increased.

Relief of muscle spasm and pain which the use of curare affords in the treatment of periarthrititis of the shoulder and low back pain is dramatic. It would be unsound, of course, to discard other proved therapeutic measures specifically applicable to the underlying pathologic lesion. The contribution of curare is the abolishment of the cycle of muscle spasm and pain which often constitutes a most trying and protracted problem. Earlier rehabilitation of the patient is then possible.

In the treatment of osteoarthritis of peripheral joints with associated degenerative periarticular (capsular) fibrositis, curare is generally unsatisfactory. Since the restriction of mobility and pain in these cases is related largely to changes in the joint cartilage and articular capsule and not primarily to reflex muscle spasm, the absence of a favorable response to therapy with curare is not surprising.

Curare has also proved totally ineffective in the syndrome of fibromyositis.

The lack of benefit to be derived from the use of curare in cases of psychogenic rheumatism merely serves to define more sharply the specific problems in which it may be helpful.

Reactions followed the administration of curare in 12 of the 58 patients. For the most part reactions were mild and not disabling, and consisted of

ness. Prostigmine, an antagonist to curare, may be employed to overcome the more severe reactions.

#### BIBLIOGRAPHY

1. SCHLESINGER, E. B.: The use of suspension of tubocurarine in oil in the treatment of spasticity, *Arch. Neurol. and Psychiat.*, 1946, lv, 530.
2. SCHLESINGER, E. B.: Recent advances in the use of curare in clinical practice, *Bull. N. Y. Acad. Med.*, 1946, xxii, 520.
3. SCHLESINGER, E. B.: Curare: a review of the therapeutic effects and their physiological basis, *Am. Jr. Med.*, 1946, l, 518.
4. SCHLESINGER, E. B., and RAGAN, C.: "Muscle spasm" in acute low back pain and similar syndromes, *Am. Jr. Med.*, 1946, l, 621.
5. SCHLESINGER, E. B.: Therapeutic applications of curare and their physiologic implications, *N. Y. State Jr. Med.*, 1947, xlvii, 1689.
6. STEINER, G., FREUND, H. A., LICHENTRITT, B., and MAUN, M. E.: Lesions of skeletal muscles in rheumatoid arthritis. Nodular polymyositis, *Am. Jr. Path.*, 1946, xxii, 103.

well, requiring only 20 to 30 units of insulin per day) some 20 others have been reported.

In these radical procedures, the operative risk, the long term followup, and the comfortable physiology and relief from pain and jaundice depend upon several factors: (1) the type of the carcinoma, (2) the site of the tumor, (3) the early diagnosis of the lesion, before it has spread to the lymph nodes and peritoneum, (4) the radical, en bloc, removal of the growth with part or all of the pancreas, the entire duodenum, the lower end of the common duct, the antrum of the stomach, and the retroduodenal and pancreatic lymph nodes.

### THE TYPE OF CARCINOMA

Carcinoma of the papilla of Vater and the ampullary area is usually a fungating adenocarcinoma, growing into the lumen of the duodenum with a slower invasion of the lymphatics. Carcinomas of the pancreas are more often of the invasive, infiltrating, undifferentiated type, spreading rapidly into the lymph nodes and metastasizing to the liver and peritoneum.

### THE SITE OF THE TUMOR

Ampullary growths obstruct the bile and pancreatic ducts more quickly and completely than those in the pancreas, and give the important warning signal of jaundice earlier. Courvoisier's syndrome of painless jaundice with an enlarged gall bladder is most frequently seen in the patients with ampullary tumors. However, not all of these patients are pain-free, yet the pain is not as severe, constant, or radiating to the back as it is in pancreatic carcinomas of the body or tail.

In carcinoma of the pancreas, the warning signal of jaundice depends upon the proximity of the growth to the common duct. It is usually absent in carcinoma of the body and tail. Pain, as mentioned, is usually more severe and constant, worse on lying down and frequently of a boring character, radiating into the back. The more distant from the ampulla, the later the diagnosis as a rule, and the worse the prognosis.

### EARLY DIAGNOSIS

Aside from the essential history and physical examination, which in many patients establishes the early diagnosis, certain laboratory procedures are helpful and must be emphasized. The most important is the study of the duodenal contents. This is based upon the early sound observations of Pavlov,<sup>6</sup> who demonstrated the effect of increased pancreatic external secretion by vagal stimulation, and of Bayliss and Starling,<sup>7</sup> who demonstrated the hormonal action of secretin in accelerating the flow of pancreatic juice. Since then, Lagerlöf<sup>8</sup> in Stockholm, Comfort<sup>9</sup> and his associates at the Mayo Clinic, and Bauman<sup>10</sup> at the Columbia-Presbyterian Clinic in this country have demonstrated the value of duodenal intubation in the differen-

patients lived five years or more, after removal of ampullary growths—two of them over seven years. Of the collected cases of carcinoma of the pancreas, three have survived five years or more,—two of them operated upon by Brunschwig.<sup>14</sup> One of these, the first one stage radical resection for carcinoma of islet cells, is living over nine years, but may have liver metastases at present. This is not a functioning islet cell tumor, however. In Cattell's<sup>11</sup> largest series of 59 patients operated upon for carcinoma, 30 per cent lived three years or more.

The fact that it has been demonstrated that cancer cells can be readily found in pancreatic duct fluid in cases of pancreatic carcinoma, and that trypsin favors the transplantation of cancer cells in experimental animals<sup>15</sup> would explain the high incidence of recurrence in resection of the pancreas, and may be a definite indication for a total pancreatectomy in patients with carcinoma of the pancreas.

#### BIBLIOGRAPHY

1. KAUSCH, W.: Das Carcinom der Papilla duodeni und seine radikale Entfernung, *Beitr. klin. Chir.*, 1912, lxxviii, 439-486.
- HIRSCHEL, G.: Die Resektion der Duodenums mit der Papille wegen Karzinoms, *München. med. Wchnschr.*, 1914, lxi, 1728.
- TENANI, O.: Contributo alla chirurgia della papilla del Vater, *Policlinico*, 1922, xxix, 291.
2. HOWLAND, G., CAMPBELL, W. R., MALBY, E. J., and ROBINSON, W. L.: Dysinsulinism; convulsions and coma due to islet cell tumor of pancreas, with operation and cure, *Jr. Am. Med. Assoc.*, 1929, xciii, 674-679.
3. WHIPPLE, A. O., PARSONS, W. B., and MULLINS, C. R.: Treatment of carcinoma of the ampulla of Vater, *Ann. Surg.*, 1935, cii, 763.
4. WHIPPLE, A. O.: Pancreatoduodenectomy for islet cell carcinoma: a five year followup, *Ann. Surg.*, 1945, cxxi, 847.
5. PRIESTLEY, J. T., COMFORT, M. W., and RADCLIFFE, J.: Total pancreatectomy for hyperinsulinism, *Ann. Surg.*, 1944, cxix, 211.
6. PAVLOV, J. P.: Die Arbeit der Verdauungsdrüsen, 1898, Wiesbaden.
7. BAYLISS, W. M., and STARLING, E. H.: The mechanism of pancreatic secretion, *Jr. Physiol.*, 1902, xxviii, 325.
8. LAGERLÖF, H. O.: Pancreatic function and pancreatic disease studied by means of secretin, 1942, P. A. Norstedt and Söner, Stockholm.
9. COMFORT, M. W., PARKER, R. L., and OSTERBURG, A. E.: Concentration of pancreatic enzymes in the duodenum of normal persons and persons with disease of the upper abdomen, *Am. Jr. Digest. Dis.*, 1939, vi, 249.
10. BAUMAN, L., and WHIPPLE, A. O.: The diagnostic value of pancreatic function tests in 47 surgically treated patients, *Am. Jr. Med. Sci.*, 1944, ccvii, 281.
11. CATTELL, R. B., and PYRTEK, L. J.: An appraisal of pancreatoduodenectomy: a followup study of 61 cases. Read before the Southern Surgical Association Meeting, Dec. 6, 1948; to be published in *Ann. Surg.*, 1949. Also personal communication, March 8, 1949.
12. LOCKWOOD, J. S.: Personal communication, March 28, 1949.
13. WAUGH, J. M.: Personal communication, March 15, 1949.
14. BRUNSCHWIG, A.: Personal communication, March 20, 1949.
15. HOWES, E. L.: Experiments not yet published. Quoted by Dr. Lockwood.

period of observation of these patients was often shorter than desirable, so that in many instances the daily dose of insulin was considerably more at the time of dismissal than it subsequently became at home, and the control of glycosuria in some instances was not the best attainable.

The fact that the response of diabetic patients to treatment differs is frequently overlooked. That such variability actually exists is illustrated by the well-known fact that in almost half of all cases of diabetes the disease is well controlled by diet therapy alone, while in the other half insulin in addition to diet is necessary. Furthermore, among patients who require insulin there is a great variability in response to treatment. The reasons for this variability are not well understood. It may perhaps indicate that there are different forms of the disease, different etiologic factors, or possibly only differences in the intensity of the disease. In any event, it is important to be aware of the inherent ease or difficulty of therapy in different diabetic patients before a program of administration of insulin is chosen in any given case, and before the merits of any particular system of therapy employed in a group of cases are judged.

Stated simply, in some diabetic patients the disease is easily controlled by almost any program of administration of insulin, whereas in others the timing characteristic of the action of the insulin employed must be carefully tailored to the needs of the individual. In the latter group of cases a relatively intense insulin action usually is needed during the day when food is being ingested, and a relatively feeble insulin action, during the fasting hours of the night. Insulin therapy to be effective in cases of severe diabetes must be arranged so that account is taken of the fact that the human subject eats during the day and fasts during the night. Furthermore, there is a small group of patients—those who have so-called unstable or brittle diabetes—in whom it is virtually impossible to maintain sugar-free urine and freedom from insulin reactions with any type or combination of insulins now available. In this group it seems that nothing short of an “automatic” insulin, with rate of absorption determined by the level of the blood sugar, would accomplish precise control. Unfortunately, there is at present no indication that an insulin with such a high order of intellect will ever be developed.

#### DEVELOPMENT OF THE USE OF MIXTURES OF INSULIN

In this country Colwell,<sup>2</sup> MacBryde,<sup>3</sup> Peck<sup>4</sup> and others have made intensive studies of the action of mixtures of regular and protamine zinc insulin in diabetic patients. Colwell,<sup>2</sup> in particular, in a series of excellent papers published since 1942, has described with considerable precision the timing characteristics of mixtures of varying proportions of regular and protamine zinc insulin. Briefly, it has been shown that it is necessary to mix at least one part of regular with one part of protamine zinc insulin to secure definite modification of the action of the latter. Intensification and shortening of action is not sufficiently marked to be therapeutically useful

well's descriptions of their action, arrived at by rigidly conducted experimentation.

One further digression is necessary before proceeding to a consideration of the treatment employed in our recent group of cases. This concerns the vexing questions of what constitutes control of diabetes and, once control has been defined, how important is it? Is it necessary to set one's therapeutic goal any higher than the simple avoidance of ketosis and severe insulin reactions? These questions have not yet been answered satisfactorily, and he who pretends to know the answer is basing his opinion more on feeling than on actual knowledge. I am personally of the opinion that control (or lack of it) is probably not the only, or even the crucial factor in the prevention (or development) of the so-called degenerative complications of diabetes, arteriosclerosis, retinopathy, neuropathy and intercapillary glomerulosclerosis, which are being observed with increasing frequency among diabetic patients who have been kept alive for many years by use of insulin. Nevertheless, as Ricketts<sup>6</sup> has pointed out, the burden of proof is on the one who says that control is unimportant. Prolonged periods of unbridled glycosuria, perhaps associated at times with mild ketosis, might well be one factor in the development of degenerative complications, even if not the sole factor. Therefore, until the contrary is proved, we should continue to strive for as precise control of glycosuria as is possible and compatible with a reasonably simple program of treatment and the avoidance of insulin reactions.

#### TYPES OF INSULIN THERAPY RECENTLY EMPLOYED

Now to proceed to a consideration of the types of therapy employed in the recent group of 246 ambulatory diabetic patients. This particular number of patients was chosen for study because it included exactly 100 patients who were treated with extemporaneous mixtures of regular and protamine zinc insulin. These 100 patients will be subjected to closer scrutiny than the rest because it is treatment with such mixtures that interests us at this time.

First, it will be noted that of the total of 246 patients, 96 (or 39 per cent) required only diet therapy, without the use of insulin, for control of glycosuria (table 1). We have made a practice of omitting insulin only in those cases in which the urine is demonstrated to remain consistently free of sugar while the patient is on an adequate diet without the use of insulin. This figure is somewhat lower than that for the total diabetic practice of the clinic,

TABLE I  
Therapy Employed Recently in 246 Cases  
of Diabetes Mellitus (1948-1949)

Therapy	Cases	Per cent
No insulin	96	39
Insulin	150.	61

experience, these same patients get along equally well with mixtures, and we believe more safely. Indeed, it seems that all patients now treated with protamine zinc insulin would fare equally well with an insulin having timing characteristics intermediate between those of protamine zinc and regular insulin.

It has already been pointed out that in the early days of the use of mixtures it was found by a rather tedious process of clinical trial and error that the best control of severe diabetes and the greatest freedom from insulin reactions were attained with mixtures containing 2 or 3 units of regular insulin for every 1 unit of protamine zinc insulin. The experience of recent years has continued to verify this early impression. The strong effect of such mixtures tends to prevent excessive glycosuria during the day, while the prolonged effect prevents escape from control overnight. There is sufficient

TABLE IV  
Mixtures of Regular and Protamine Zinc Insulin  
in 100 Cases of Diabetes Mellitus

Ratio of regular to protamine zinc insulin	Cases
Less than 1:1	2
1:1 to 1.5-:1	4
1.5:1 to 2-:1	19
2:1 to 2.5-:1	54
2.5:1 to 3-:1	13
3:1 and higher	11

overlapping of the effects of doses on successive days to provide additional insurance against serious loss of control due to the waning of action of one dose before the next one begins to act. The more severe the diabetes, or the higher the carbohydrate content of the diet, the more likely is the ratio to be in the neighborhood of 3:1 rather than 2:1. It will be noted that for 67 of the recent series of 100 patients treated with mixtures, the ratio of regular to protamine zinc insulin was between 2:1 and 3:1 (table 4). With longer periods of observation of the patients the proportion of mixtures in this range would probably be increased, for many of the patients who had mild diabetes and used low ratios at the time of dismissal eventually were stabilized on small doses of protamine zinc insulin alone.

#### DIFFICULTIES IN THE USE OF MIXTURES

It is perhaps unnecessary to point out that mixtures do not solve all the problems of treatment of patients who have diabetes of the type which has been described as "brittle," "labile" or "unstable." The diabetes of a few of these patients remains difficult to control with mixtures or any other form of insulin therapy. While these patients have the most severe type of diabetes from the standpoint of difficulty of control, they do not necessarily

more, it can be expected to give satisfactory results in all the patients who are now successfully treated with small doses of protamine zinc insulin alone. In the few cases of severe diabetes in which higher ratios of regular to protamine zinc insulin are required, supplementation with additional amounts of regular insulin is easily accomplished in accordance with the needs of the individual patient. Fortunately, the addition of small amounts of regular insulin to insulin type NPH 50, unlike the addition to protamine zinc insulin, results in definite intensification of its action.

The principles involved in the adjustment of the two kinds of insulin comprising a mixture are relatively simple. In the first place, as has already been mentioned, it was learned by experience some time ago that the majority of patients who are treated with mixtures of insulin obtain the best control when the amount of regular insulin is two to three times the amount of protamine zinc insulin. In the actual regulation of diabetes of a patient, one can proceed as follows: The test for sugar in a fresh specimen of urine voided in the morning before breakfast is used as a criterion of the adequacy of the dose of protamine zinc insulin taken 24 hours previously. The dose is so adjusted that there will be no nocturnal reactions, and little or no sugar in this specimen, preferably none. Likewise, the test of a fresh specimen voided late in the afternoon before supper serves as an index of the adequacy of the dose of regular insulin taken that morning. This dose is adjusted so that reactions will not occur during the day, and there will be no more than a trace of sugar in this specimen. Changes in the dose of protamine zinc insulin are usually made in steps of 2 units, since this dose is relatively small, while changes in the dose of regular insulin, which is usually at least twice as large, are usually made in steps of 4 units. The patients are carefully instructed in the method of adjustment, for frequently further adjustments of the dose are necessary at home, particularly if the period of observation under the direct supervision of the physician is short.

### SUMMARY

The timing characteristics of appropriate mixtures of protamine zinc and regular insulin are well adapted to the needs in many cases of moderately severe to severe diabetes. Such mixtures provide the requisite intensity of insulin action during the day when food is being ingested, and a prolonged action of low intensity for maintenance of control of diabetes overnight. An effective proportion in most instances is between 2 and 3 units of regular insulin to 1 unit of protamine zinc insulin.

A fixed modification of protamine zinc insulin having an action like that of a 2:1 mixture of regular and protamine zinc insulin such as insulin type NHP 50, could be employed with satisfactory results in many more cases than the standard protamine zinc insulin which is now available. Its action could be further intensified and shortened by the addition of regular insulin when necessary.



# SUMMARY OF EVIDENCE RELATING LIFE SITUATION AND EMOTIONAL RESPONSE TO PEPTIC ULCER \*

By STEWART WOLF, M.D., *New York, N. Y.*

THE evidence connecting the occurrence and recurrence of peptic ulcer to emotional conflicts in the life situation has been recently reviewed by Wener and Hoff.<sup>1</sup> The relationship has not as yet been definitely established, but on the basis of studies from several points of view and with a variety of technics, it seems highly likely that some peptic ulcers, at least, occur as part of a biologic pattern which is set in motion in reaction to stresses and strains involving chiefly problems of interpersonal relationship. The data in support of this view are outlined briefly below.

First, it has been known for many years that the stomach of the subject with duodenal ulcer is a hyperfunctioning one, that is, it is red, secretes relatively large amounts of acid, is relatively hypermotile and empties in a comparatively short time. When it has been possible to induce experimental peptic ulcer in animals, the condition has been preceded and accompanied by intense engorgement of the gastric mucosa.<sup>2, 3, 4</sup>

In our studies on the fistulous subject, Tom, we found by direct observation of the gastric mucosa and simultaneous collections of gastric juice and recording of motility that this hyperfunctioning state could be induced by situations which engendered anxiety associated with feelings of hostility and resentment.<sup>5</sup> We found, moreover, that the stomach under these circumstances was hyperemic, turgid and engorged. When, under circumstances of sustained resentment, this pattern of gastric hyperfunction was prolonged, the pain threshold of the stomach was significantly reduced. This led to localized epigastric pain following the application of stimuli such as pinching or Faradic current, which were ordinarily non-noxious. Likewise, gastric contractions of a force and magnitude which would ordinarily not arouse sensations became painful. Thus, in the absence of ulceration but in the presence of sustained gastric hyperemia and hyperfunction, the characteristic ulcer symptoms of epigastric pain relieved by food or alkalis were frequently observed.

Not only was lowering of the pain threshold observed to accompany gastric hyperfunction in association with sustained conflict, but a second physiologic hazard was also observed under these circumstances, namely, increased fragility of the mucous membrane. When the stomach was in an

\* Presented at a Panel Discussion, Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 29, 1949.

From the Department of Medicine of Cornell University Medical College and the New York Hospital, New York, N. Y.

Aided by grants from the Commonwealth Fund and the Estate of Lester N. Hofheimer.

gical procedures considered to have divided all of the parasympathetic innervation to the stomach. Additional confirmation derives from an experiment performed in our laboratory on a second fistulous subject whose fistula was made prior to the attempted surgical removal of a carcinoma of the esophagus.<sup>7</sup> During the latter procedure, it was necessary to section the vagus nerves above the diaphragm. Thus, direct observations were available on the stomach before and after vagotomy. Experimental procedures similar to those performed on Tom were carried out on this subject, his gastric mucosa being viewed through a Brown-Buerger cystoscope. During one of the experimental periods prior to vagotomy the appearance and manner of the subject indicated a sharp change from his usual, quiet friendliness. His face was red, and he appeared exasperated and irritable. He had complained of stiffness and back pain ever since the previous experiment, and confessed that he was angry at having come down to the laboratory again in view of the apparent delay occasioned in his operation.

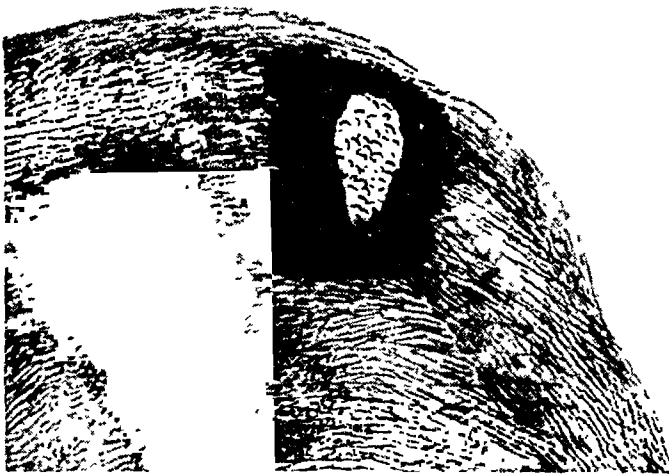


FIG. 1. Drawing of ulcerated lesion induced experimentally on the gastric mucosa of Tom.

The subject's stomach was examined and found to be much redder and more engorged than before, about 70 on the scale in contrast to the previous 50. He was more voluble and talkative. Asked about his concern regarding his condition, he said that he was reminded of the first doctor whom he had consulted for difficulty in swallowing. The latter had focused his attentions on the stomach, much to the annoyance of the patient. "He was so dumb. I told him it wasn't my stomach, because I knew I couldn't swallow right. He made me waste four weeks fooling around." On this occasion, there occurred much more spontaneous motor activity in the stomach than before. The mucous membrane was so turgid that the minor traumata incident to the instrumentation with the cystoscope caused bleeding. The subject's dominant mood during this interview was anger coupled with hostility and strong feelings of frustration. His stomach displayed the pic-

transitory and even sustained alterations in gastric function occur in company with emotional conflicts and that such changes may be associated with epigastric pain, it remains to correlate such reactions to stress with gastric changes and symptoms in subjects with the actual clinical peptic ulcer. The coincidence of onset and exacerbation of the ulcer syndrome in association with difficult life situations is a familiar bedside observation. Mirsky and associates have shown an increase in concentration of a proteolytic enzyme in the blood and urine of subjects with peptic ulcer and especially in situations of significant personal conflict.<sup>9</sup> Experimental correlation of conflict with gastric hyperfunction and symptoms was reported by Mittelman and Wolff<sup>10</sup> and more recently additional evidence on this point has been collected as detailed below.

*Case 1.* A 44 year old civil service employee had complained of gnawing epigastric pain on and off for 20 years. His father had been a gentle, retiring person and his mother a matriarchal woman, intensely ambitious for her children. His two older brothers were able to adjust satisfactorily to this setting, the oldest by graduating from medical school, the second one by adopting a rebellious attitude and becoming a professional gambler instead of a lawyer as his mother had wished. The patient felt the need to compensate for his brother's indifference, and took pre-medical work in college. He did poorly, and tried engineering instead. After failing that, he abandoned college. In this setting, he had his first symptoms of epigastric pain, and a duodenal ulcer was demonstrated by radiologic examination. He later obtained a civil service job as a draftsman, and became engaged to a warm, sympathetic girl. Symptoms disappeared during this interval, until the girl died of rheumatic heart disease a few months later. The patient's mother also died at approximately the same time. Within a few months he married an authoritarian, cold and financially ambitious woman. She disapproved of his social relationship with men friends, and eventually forced him to give up lodge activities, from which he derived great satisfaction. Shortly after his marriage, the patient's ulcer symptoms recurred, and they have remained chronic ever since. Several exacerbations and two episodes of hemorrhage have coincided with periods in which his wife seriously disparaged his competence as a man. The following experiment, shown graphically in figure 3, illustrates the relevance of his conflicts concerning his wife to his gastric disturbance.

Ten minutes after the end of a spontaneous period of vigorous gastric motor activity and during a period of almost complete absence of contractions, an interview was undertaken in which the patient was reminded that, in contrast to the high regard in which he had been held by his lodge associates, his wife considered him inadequate as a provider, companion and sexual partner. He became grim and tense, clenched his jaws frequently and said, "it's been a fight all along, and now I got no more fight left in me. I'm caught like a rat in a trap." Promptly, forceful gastric contractions began, and by the end of the interview, a state of incomplete tetanus had been established. Acid secretion was also greatly enhanced, exceeding the level observed during the earlier period of spontaneously increased gastric function. By this time, the subject had begun to groan with pain. Shortly thereafter, during attempts at reassurance and diversion, the evidences of gastric hyperfunction subsided, and with them the symptoms.

*Case 2.* A 34 year old Italian income tax collector had his first episode of ulcer pain at age 16 in a setting of conflict with his father over retaining a job as auto paint sprayer, which he considered beneath his capabilities. The patient had resented his father from an early age. "My earliest recollection is lying awake at night worrying and thinking about the way my father was making sexual advances toward

my mother. I was always relieved if I saw my father go to bed first and my mother stay in the kitchen." The father was a cold, irascible individual who shared the "old country" point of view that a man's sons should work to support him as soon as they could be taken from school. The patient, on the other hand, was eager to go through college and become an engineer. He had grown up in a neighborhood in which there were a good many Jews, and it was a common pattern among the Jewish parents to make unusual sacrifices to provide professional education for their children. Both the patient's father and his younger brother, who also was caught in a conflict between the cultural pattern of his father and his neighborhood, developed peptic ulcers. In addition to his limited educational opportunities, the patient felt that another serious handicap was his small stature. He effected a truculent manner as a child, and got into a great many fights, which he considered "prophylactic," as a means of avoiding being "pushed around" by other people. He could not bear to be laughed at, and was especially sensitive to any slight, real or imagined, to his dignity and competence. He finally obtained a job as an income tax collector, and married an ambitious woman. They had one daughter. He always had difficulty satisfying his wife sexually because of premature ejaculation. She was also dissatisfied with his fixed earnings and lack of progress in the civil service job. The patient noted epigastric pain off and on with exacerbations during periods of stress and conflict and remissions during periods of relative security. "It makes me worse if anyone crosses me. I tighten up and my stomach hurts. When I can relax my stomach improves." He had a gastrointestinal hemorrhage which occasioned admission to the hospital, when a conflict developed between his wife and his favorite sister. During his period of hospitalization he improved markedly with rest, reassurance and without special attention to diet except for frequent feedings. During an asymptomatic period he was intubated with a recording balloon and a Levine tube for collection of the gastric juice. Specimens were withdrawn every 15 minutes. Free and total acid were determined by the usual colorimetric technics. Hydrochloric acid production was calculated with recourse to the methods of Hollander described elsewhere.<sup>5</sup> The acid values and motility pattern are recorded in figure 4. Fifteen minutes after a period of spontaneous motor activity at a time when the gastric musculature is relatively refractory, a discussion was begun of a humiliating experience which he had had on the ward. "An Italian fellow called me a name in Italian. I'm not a dope that I have to take that. He did it again. Later in the day I was lying in bed with a pain and he said 'This is a hell of a time for you to be lying in bed.' I told him it was none of his business, and not to bother me. Now he won't speak to me, and that's what I want. I think I'm entitled to the same respect I give out. Whenever anyone makes a crack at me I have two of them to throw back. I think I'm pretty sharp about solving problems." During the discussion, he was tense, restless and red-faced. Vigorous motor activity occurred and increase in acid output associated with epigastric pain. After approximately 25 minutes, the patient was strongly reassured and the conversation was turned to diverting topics. The gastric motor activity stopped and the pain subsided.

*Case 3.* A 47 year old Jewish lawyer had had peptic ulcer for 23 years. He was the only child of Russian immigrant parents. The father was a quiet, reflective, religious man, but the mother was intensely ambitious and hard-working. She and the father made severe financial sacrifices to provide the patient with an education. He did well in college and law school, and during the course of these years he changed his name to a more easily pronounced, anglicized form. He also married a Roman Catholic girl. His parents disapproved of this marriage, but condoned it, their principal concern being their son's "success in his career." Shortly after graduation from law school, he was taken into a firm of all gentile lawyers. He soon became heavily relied upon, and was doing much of the difficult work of the office. The partners persistently failed, however, to admit him to the firm. This was the source of great disappointment

and frustration, not only to himself but to his mother and wife, who, like his mother, was intensely ambitious. It was in this setting that ulcer symptoms first developed.

Finally, when it appeared that the partners could no longer exclude him from the firm, they hired a second Jewish lawyer. The head of the firm then told the patient that he felt unjustified to take one of these men and not the other into the firm. This occasion was followed by a severe episode of gastrointestinal bleeding, for which the patient was hospitalized. Finally, at the outbreak of World War II, the younger Jewish lawyer was taken into the Army. The older members of the firm were often preoccupied with matters outside the office, and thus the patient's duties and responsibilities were redoubled. He was virtually running the law office. Despite the heavy work and long hours, his ulcer symptoms disappeared, and throughout the period of the war he felt well. At the conclusion of the war, however, his associate returned from service unharmed, and again the frustrating situation was resumed. The patient's epigastric pain recurred and became incapacitating, and again he was admitted to the hospital. After a few days of rest, encouragement and strong reassurance, and while taking alkalis and frequent feedings, his symptoms again subsided.

At this point, he was intubated with a balloon attached to a kymograph. Gastric motor activity of an average type was recorded until suddenly an interview was engaged in in which the patient was asked why he had failed to meet his mother's ambitions and whether or not he felt that her sacrifices in his behalf had been justified. Almost immediately, gastric contractile activity became enhanced. He showed no evidence of tension or "nervousness" at first. He gave a restrained, well-organized and forceful justification of his life. As the account proceeded, however, his voice became stronger, and he became restless and tense, and the gastric contractions were associated with localized epigastric pain. The interview was allowed to continue for one hour and 30 minutes, when he was given 0.3 gm. of sodium amytal intravenously. At this point, gastric contractions stopped abruptly. His pain was promptly relieved, and his entire manner was altered. He clung weeping and sobbing to the examiner's hand, saying "I've tried so hard, so hard." He said that he finally felt relaxed, and was weeping with relief. After 27 minutes of freedom from pain, and while still under the influence of sodium amytal, a second interview was begun in which it was suggested that his change of name, his marriage to a Roman Catholic and his association with a gentile firm might represent an attempt to escape from identification with Judaism. Again his manner became restrained, his flow of conversation even and forceful. Gastric contractions were resumed, and although they were of much smaller magnitude, they were nevertheless painful.

*Comment.* These experiments on subjects with peptic ulcer in which painful gastric hyperfunction was induced or interrupted by appropriate manipulation of the situation established fairly clearly a relationship between the gastric disturbance and the attitudes and emotions of the subjects. They indicate that these individuals react habitually to stress with an acceleration of gastric function. They do not prove that peptic ulcer is caused by such sustained gastric hyperfunction, but they support this view. Further data were adduced from study of a fistulous human subject who happened also to have a peptic ulcer.

*Case 4.* A 67 year old Merchant Marine tug boat chief engineer developed obstructive symptoms with persistent vomiting and emaciation three weeks prior to his admission to the hospital. He had noted weakness and vague epigastric discomfort but he had had no history of pain suggestive of peptic ulcer except for a brief episode 30 years before which lasted only a few weeks. Roentgen-ray examination, however,

curred over a period of three weeks. Because of the esophageal stricture a gastrotomy was done. The stoma measured approximately 5 cm. in diameter and through it herniated parts of a few engorged gastric rugae. It was accordingly possible to study this subject in the same manner in which experimental observations were made on Tom and published in detail elsewhere.<sup>5</sup>

The experiment was carried out 13 hours after the last feeding and with the subject reclining comfortably on a couch. The gastric mucosa was continuously observed under standard lighting conditions. Gastric juice was siphoned through a Levine tube and motor activity was recorded on a kymograph from an inlying inflated balloon. During approximately 45 minutes of control period the subject was lightly diverted and continuously reassured. As already noted the membrane during this period was already moderately engorged (3+) and hyperemic (60 on the color scale). Gastric juice was elaborated at the rate of approximately 20 c.c. every 15 minutes, was moderately viscous and opaque with free acid remaining in the neighborhood of 15 units. Abruptly he was asked whether or not his own and his wife's ambitions had been satisfied by his becoming a tugboat engineer. His manner became serious and slightly grim, but he maintained that the work had been entirely satisfactory. He was then asked where a tugboat engineer stood in the social constellation of men who had qualified as chief engineers. His even manner continued although tension was evident by this time and he wiped a tear from each eye. He was further asked about possible conflicts with his wife. He denied conflicts but the denial was associated with additional lacrimation and within one-half hour of the start of this interview the gastric rugae had become intensely red (80) and engorged, completely filling the area of the stoma. Motor activity became intense and sustained and free acid rose to 35 units. No pain was noted.

*Comment.* This experiment provides direct visual confirmation of the findings detailed above in patients with peptic ulcer in whom the contemplation of relevant personal conflicts was associated with intense gastric hyperfunction and often symptoms.

*Nature of the Personality Reaction.* Numerous attempts have been made to explain why some individuals in a setting of significant emotional conflict develop troublesome gastric hyperfunction and perhaps peptic ulcer, while others may develop precisely the opposite changes in the stomach with hypoacidity, slow emptying and nausea and still others develop other physiologic disturbances but no evidence of gastric disorder. Analysis of the conflict situation has not been fruitful, and neither have attempts to construct a constitutional or personality profile been successful in delineating very sharply between those who develop and those who do not develop peptic ulcer. It has been more profitable to examine and characterize the way in which the individual habitually met threats and challenges in his life situation. The subject with peptic ulcer may feel passive and have strong dependent needs as has been pointed out by Alexander<sup>11</sup> and numerous others,<sup>8, 12, 13</sup> but his behavior is aggressive. He must appear master of the situation in contrast to the subject with gastric hypofunction, who readily assumes a passive rôle in human relationships.<sup>14</sup> The gastric hyperfunction itself implies a need to be fed and sustained, but it is an aggressive biologic response which in animals including man precedes the act of devouring. It is thus in keeping with the general behavior reaction of competitive aggression. These features have been reviewed elsewhere.<sup>5, 10, 11</sup> One probably could not answer in simple

5. WOLF, STEWART and WOLFF, H. G.: Human gastric function. An experimental study of a man and his stomach, 2nd ed., 1947, Oxford University Press, New York.
6. PALMER, W. L.: Mechanism of pain in gastric and in duodenal ulcer, *Arch. Int. Med.*, 1927, xxx, 109.
7. WOLF, STEWART and ANDRUS, W. D.: The effect of vagotomy on gastric function, *Gastroenterology*, 1947, viii, 429.
8. SZASZ, T. S., KIRSNER, J. B., LEVIN, E., and PALMER, W. L.: The role of hostility in the pathogenesis of peptic ulcer: Theoretical considerations with the report of a case, *Psychosom. Med.*, 1947, ix, 331.
9. MIRSKY, I. A.: Title at Am. Psychosom. Soc., *Psychosom. Med.* In press.
10. MITTELMANN, B., and WOLFF, H. G.: Emotions and gastroduodenal function, *Psychosom. Med.*, 1942, iv, 5.
11. ALEXANDER, F.: Clinical notes: Treatment of a case of peptic ulcer and personality, *Psychosom. Med.*, 1947, ix, 320.
12. HEIDE, CAREL VAN DER: A study of mechanisms in two cases of peptic ulcer, *Psychosom. Med.*, 1940, ii, 398.
13. DUNBAR, FLANDERS: Emotions and bodily changes, 1946, Columbia University Press, New York.
14. WOLF, STEWART: Observations on the occurrence of nausea among combat soldiers, *Gastroenterology*, 1947, viii, 15.
15. WOLF, STEWART, PFEIFFER, J. B., RIPLEY, H. S., WINTER, O. S., and WOLFF, H. G.: Hypertension as a reaction pattern to stress; summary of experimental data on variations in blood pressure and renal blood flow, *Ann. Int. Med.*, 1948, xxix, 1056.

## CASE REPORTS

*Case 1.* A 43 year old Irish-Hawaiian male was first admitted to Queen's Hospital July 12, 1945, with a chief complaint of weakness. He had diabetes and had been taking insulin "off and on" for one year. During this period he had developed a persistent diarrhea, had lost about 70 pounds, and had become very weak. He described his stools as being large and yellow, with "droplets of oil" on the surface of the water after an evacuation.

His past history included measles, mumps, and chickenpox in childhood, and pneumonia at the age of 27. The only previous gastrointestinal disturbances he had ever experienced were three bouts of severe epigastric pain many years previously, which the patient attributed to over-indulgence in alcohol. His father had had diabetes and died at the age of 54. His mother had died of a "stroke" at the age of 72. There was no other history of diabetes in the family

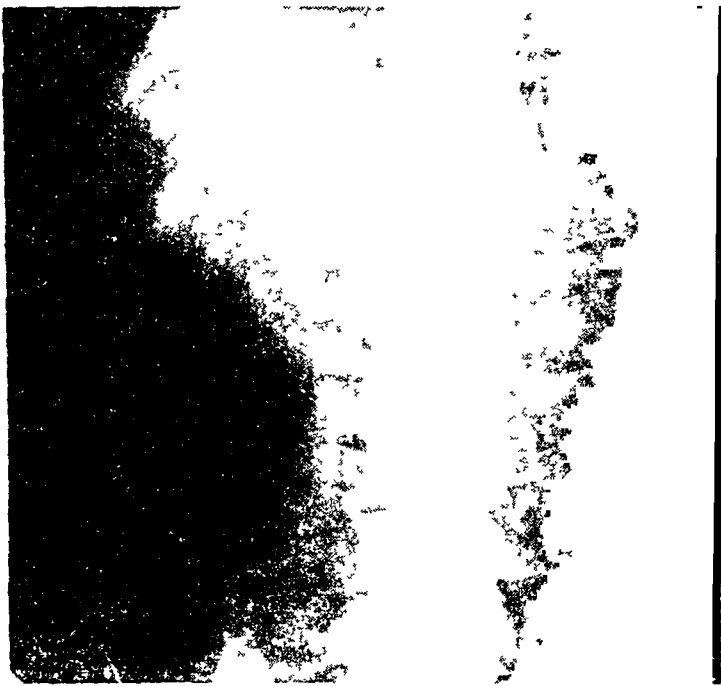


FIG 1. Roentgen-ray of the abdomen, case 1, showing multiple calcifications in the head and tail of the pancreas.

Physical examination revealed a tall, gaunt male who appeared chronically ill. There were slight reddening and atrophy of the tongue, and tiny fissures at the corners of the mouth. The remainder of the examination was essentially negative except for evidence of rather marked weight loss. Admission blood count showed 5,180,000 erythrocytes, 13 gm. of hemoglobin, and 16,150 leukocytes, with 42 per cent polymorphonuclear leukocytes and 58 per cent lymphocytes. The urinalysis was negative and the blood sugar was 158 mg. per cent. A stool examination showed a large number of striated muscle fibers and 16 per cent of the dry weight was fat.

A barium enema revealed a normal colon but the roentgenologist noted a large accumulation of calcific deposits in the pancreas. A lateral film of the abdomen confirmed the location of the calcifications. An oral cholecystogram demonstrated a normal gall-bladder. An upper gastrointestinal roentgen-ray study was essentially negative except for a slight compression of the descending and transverse portions of the duodenal loop from without, apparently by the head and body of the pancreas.



calcium was 9.4 mg. per cent and the blood phosphorus was 2.8 mg. per cent. The blood Laughlen test was negative. Blood amylase was 10 per cent (Fennel's method: 10 per cent to 35 per cent is normal), and the urinary amylase was 2 per cent. A roentgenogram of the abdomen again demonstrated the multiple pancreatic calcifications, and a chest film showed bronchiectasis of the left lower lobe with an associated pleural reaction obliterating the corresponding diaphragm.

Carbohydrate metabolism was still erratic and great difficulty was encountered in stabilizing his diabetes. As he gained weight, however, his insulin requirement gradually decreased from 110 to 40 units of insulin daily. He was given kapectate and at times paregoric for his diarrhea, as well as pancreatin, one gram three times daily. Amphogel was effective in relieving the sporadic epigastric pain of which he complained. He improved slowly, the cough disappeared, and his weight increased to 146 pounds. He was discharged April 18, 1946.

*Third Admission.* The patient was readmitted July 10, 1946, with a chief complaint of hemoptysis. He had felt well until about 10 days prior to admission, when he contracted a "cold." He developed a cough productive of yellow sputum which later became blood-tinged. A few moist râles at the left apex were the only new finding on physical examination. The blood count was normal except for a slight leukocytosis (11,200), with a normal differential, and the urinalysis was negative except for a four-plus sugar reaction. The blood sugar was 196 mg. per cent. The sputum contained large numbers of tubercle bacilli, and a chest film demonstrated a small reticulated infiltration in the upper lobe of the right lung. A right phrenicotomy was done September 11, 1946, and one week later the sputum was negative for acid-fast bacilli on three successive examinations. His diabetes remained difficult to control and a day-to-day variation of the insulin dosage was necessary. Steatorrhea was still present but responded fairly well to pancreatin and kapectate, and his weight increased from 134 to 144 pounds. He was transferred to a sanatorium September 28, 1946.

*Case 2.* A 39 year old white male applied for a position as chef at Queen's Hospital in August, 1946. The preemployment chest roentgenogram showed a moderately large pulmonary infiltration in the apical portion of the left lower lobe, probably tuberculous. He was admitted to the isolation unit of the hospital and put on a regimen of strict bed rest. His history revealed that he had had an increasingly productive cough for about three weeks, but no other symptoms. Physical examination was entirely negative. His blood pressure was 120 mm. Hg systolic over 78 diastolic.

There was nothing of note in his past history up to about two years before admission, at which time he had suffered a marked weight loss (approximately 70 pounds in two months), attributed by the patient to the fact that he had just had most of his teeth extracted. However, a Selective Service examination revealed that he had diabetes mellitus. He was rejected and no treatment was undertaken by the patient. Eighteen months prior to admission he had been hospitalized in Los Angeles with a bilateral pneumonia and during his stay in the hospital treatment of his diabetes was carried out. He was taking 40 units of protamine zinc insulin each morning at the time of discharge, and continued to take it regularly until his admission to Queen's Hospital. Chest roentgen-ray at the time of discharge was said to show complete resolution of the pneumonia. A short time before the patient developed this pneumonia, a close personal friend had died of pulmonary tuberculosis. There was no family history of diabetes or tuberculosis.

The sputum was positive for acid-fast bacilli. The sedimentation rate was not elevated. The blood count was normal and the urinalysis was negative. He was put on a daily dose of 55 units of protamine zinc insulin. His appetite seemed to increase steadily, but on the sixtieth hospital day his weight was the same as on ad-

revealed entirely normal spinal fluid, and an electrocardiogram on the fourth day was essentially normal except for tachycardia. A serum amylase determination on the fourth day was normal, and the serum calcium was 11.4 mg. per cent. Although his white count slowly fell to 18,000, his fever progressively mounted and he died on the fifth day without having regained consciousness. Penicillin, 50,000 units, had been given intramuscularly every two hours since admission. The clinical diagnoses were insulin shock of irreversible type, such as occurs in about 1 per cent of all patients given insulin shock therapy,<sup>7</sup> and bilateral bronchopneumonia.

At autopsy, the pancreas weighed 80 grams and felt like a bag of pebbles. On section, multiple irregular calcific nodules were found throughout, the largest measuring about 0.5 cm. across. The entire gland seemed to consist of dense connective tissue so that no parenchyma could be identified and the ducts could not be made out. Histologic study showed it to be densely fibrotic connective tissue containing only a few islands of Langerhans, a few duct-like structures, and an occasional small nest of distorted acinar cells. The many calcifications seemed to be deposited around what appeared to be areas of old fat necrosis. The islets which remained were small and in the process of being obliterated by the fibrotic process. The liver weighed 1,750 grams and was firm and smooth, with moderate passive congestion, but no fatty infiltration was detected. The gall-bladder appeared normal, emptied easily, and contained no stones. There was no evidence of fat necrosis in the mesentery or omentum. Three small superficial ulcers, which proved to be tuberculous on histologic examination, were found in the mucosa of the ileum near the ileo-cecal valve. Each lung weighed 720 grams and showed mild congestion and edema, with patchy atelectasis and lobular pneumonia. A well walled-off tuberculous abscess, 2 cm. in diameter, was present in the left apex together with a cicatrizing pleural scar. A similar lesion was found at the hilum of the left lung.

## DISCUSSION

The outstanding clinical features of these two cases of pancreatic calcification were: (1) steatorrhea with marked weight loss, (2) severe, and in one case intractable, diabetes, and (3) complicating pulmonary tuberculosis. It has been generally observed that steatorrhea occurs in only about one-half of all cases of calcareous pancreatitis. It was a prominent feature in both cases reported, although only the first patient actually complained of diarrhea. Pancreatic insufficiency could reasonably be expected from the relatively marked destruction of glandular tissue that was shown by the roentgen-ray, although disturbances of pancreatic function have been absent in about 10 per cent of the reported cases of pancreatic calcification.<sup>4</sup>

Diabetes mellitus, latent or active, is said to occur in about 50 per cent of all cases of pancreatic calcification.<sup>6</sup> This is a much higher incidence of diabetes than occurs when pancreatic damage is due to obstruction of the ducts by a pancreatic calculus. It is well known that when stones obstruct the pancreatic ducts, destruction of the acinar tissue is early, rapid, and quite complete, but the islands of Langerhans survive until very late in the process. Exocrine failure precedes endocrine failure of the pancreas when pancreatic destruction is due to ductal obstruction. No better illustration of this could be cited than the fact that Banting and Best were launched on the investigation which ultimately led to the discovery of insulin<sup>9</sup> by Barron's autopsy report on a patient who had had a pancreatic stone.<sup>10</sup> The pancreas of this

metabolic disturbances has been reported. Calcification may rarely develop painlessly (only one case in Comfort's series). Case 2 was evidently in this category.

It should, of course, be borne in mind that acute interstitial and acute hemorrhagic pancreatitis are distinct entities and may occur only once in the lifetime of an individual. That the latter and chronic relapsing pancreatitis are not identical is highlighted by the fact that diabetes has been found only rarely (2 per cent) to follow acute hemorrhagic pancreatitis,<sup>13</sup> whereas it occurs in 50 per cent or more of all cases of calcareous pancreatitis.

Complicating biliary disease is reported to be fairly common in almost all forms of pancreatic disease. A normal cholecystogram was obtained in the first case, and although abnormal function was reported in the second case, no structural abnormality was discovered at autopsy. Degenerative fatty infiltration of the liver producing a palpably enlarged liver occurs in some cases of chronic pancreatitis, the "pancreato-hepatic syndrome,"<sup>14</sup> most probably due to a deficiency in lipocaic, the pancreatic hormone which regulates the deposition of fat in the liver cells. Hepatomegaly was not present in the first case, and the liver was essentially normal on histologic study in the second case.

A history of alcoholism has often been cited as a salient feature in pancreatic inflammatory disease. It was regarded, however, as a merely coincidental finding until the accumulation of recent evidence, which has pointed to alcohol as at least a frequent precipitating agent if not actually of etiological importance. Carter<sup>15</sup> found tremendously elevated serum amylase values in 11 alcoholic patients with acute abdominal symptoms. Four of the patients were operated upon and acute interstitial pancreatitis was found. Alcohol definitely precipitated acute attacks in 14 per cent of Comfort's cases of chronic relapsing pancreatitis, and 59 per cent of his patients were users of alcohol. This has borne out the observations of earlier writers such as Weiner and Tennant,<sup>16</sup> Myers and Keefer,<sup>17</sup> and Clark.<sup>18</sup> Our first patient was a constant heavy user of alcohol, and the second patient was a sporadically heavy drinker. In a study of 4,000 autopsies, Weiner and Tennant concluded that pancreatic disease is 40 to 50 times as frequent among alcoholics as among non-alcoholics.

Patients with calcifying disease of the pancreas are predisposed to pulmonary complications, and both of our cases developed pulmonary tuberculosis. Two of Pasternack's cases and one of Snell and Comfort's also had pulmonary tuberculosis. Other pulmonary complications, such as bronchopneumonia, abscess, and gangrene have been reported. It is interesting to speculate as to whether or not the metaplasia of the bronchial epithelium resulting in these patients from the loss of vitamin A in the fatty stools<sup>13</sup> is an important factor in predisposing them to pulmonary infections. It appears that the pancreatic insufficiency not only predisposes to pulmonary infection but also has quite a direct bearing on the patient's response to it. The first patient had intractable diabetes and showed relatively little resistance to the

common duct to the stomach, duodenum, or jejunum), or external drainage by means of choledochostomy or cholecystostomy. Pain and pressure symptoms arising from pancreatic cysts which sometimes occur in chronic pancreatitis are relieved by marsupialization or internal drainage of the cysts into the small intestines. When intractable pancreatic pain is not demonstrably due to any of the above mentioned factors, more radical surgery may be necessary. Successful subtotal pancreatectomy with complete relief of pain in a small number of such patients has been reported during the past year.<sup>4, 19</sup>

### SUMMARY

1. Two cases of chronic pancreatitis with calcification, diabetes, and steatorrhea are reported.
2. Both cases were complicated by pulmonary tuberculosis.
3. The incidence, classification, pathogenesis, clinical features, and treatment of calcifying pancreatitis are briefly discussed.

### BIBLIOGRAPHY

1. PASCUCCI, L. M.: Pancreatic cyst and lithiasis, *Am. Jr. Roentgenol.*, 1944, lii, 80-87.
2. SNELL, A. M., and COMFORT, M. W.: The incidence and diagnosis of pancreatic lithiasis, *Am. Jr. Digest. Dis.*, 1941, viii, 237-243.
3. GRANEY, C. M., and REDDICK, R. H.: Calcification of the pancreas, *Am. Jr. Surg.*, 1944, lxxv, 271-275.
4. COMFORT, M. W., GAMBILL, E. E., and BAGGENSTOSS, A. H.: Chronic relapsing pancreatitis, *Gastroenterology*, 1946, vi, 239-285 and 376-408.
5. MARSHALL, W. A.: Pancreatic lithiasis, with case report and autopsy findings, *Radiology*, 1938, xxxi, 562-566.
6. FANGER, H.: Pancreatic lithiasis with associated intestinal hemorrhage, *New Eng. Jr. Med.*, 1944, ccxxxi, 678-680.
7. KALINOVSKY, L. B., and HOCH, P. H.: Shock treatments, 1946, Grune and Stratton, New York.
8. PASTERNAK, J. G.: Calcareous pancreatitis, *Ann. Int. Med.*, 1943, xix, 757-767.
9. BANTING, F. G., and BEST, C. H.: The internal secretion of the pancreas, *Jr. Lab. and Clin. Med.*, 1922, vii, 251-266.
10. BARRON, M.: The relation of the islets of Langerhans to diabetes with special reference to cases of pancreatic lithiasis, *Surg., Gynec. and Obst.*, 1920, xxxi, 437-448.
11. ELMAN, R.: Acute interstitial pancreatitis, *Surg., Gynec. and Obst.*, 1933, lvii, 291-309.
12. EDMONDSON, H. A., and FIELDS, I. A.: Relation of calcium and lipids to acute pancreatic necrosis, *Arch. Int. Med.*, 1942, lxxiv, 177-190.
13. ELMAN, R., and SACHAR, L. A.: Contributions made in 1940 to knowledge in regard to the pancreas, *Am. Jr. Digest. Dis.*, 1941, viii, 105-112.
14. ELMAN, R., and AKIN, J. T.: *Gastroenterology*, 1944, ii, 412-426.
15. CARTER, S. J.: Serum amylase findings in chronic alcoholic patients with acute, severe abdominal symptoms, *Ann. Surg.*, 1945, cxxii, 117-121.
16. WEINER, H. A., and TENNANT, R.: A statistical study of acute hemorrhagic pancreatitis, *Am. Jr. Med. Sci.*, 1938, cxcvi, 167-176.
17. MYERS, W. K., and KEEFER, C. S.: Acute pancreatic necrosis in acute and chronic alcoholism, *New Eng. Jr. Med.*, 1934, ccx, 1376-1380.
18. CLARK, E.: Pancreatitis in acute and chronic alcoholism, *Am. Jr. Digest. Dis.*, 1942, ix, 428-431.

# A SURVEY OF THE ACTUALITIES AND POTENTIALITIES OF EXFOLIATIVE CYTOLOGY IN CANCER DIAGNOSIS \*

By GEORGE N. PAPANICOLAOU, M.D., *New York, N. Y.*

IN 1925, when for the first time I had occasion to discuss with the late Dr. James Ewing, then Professor of Pathology in our School at Cornell, the possibility of using the vaginal smear as an aid in the diagnosis of uterine cancer, he asked me whether this method could be applied to endometrial as well as to cervical carcinomas. It was his opinion that such a method might prove to be of greater value in the diagnosis of adenocarcinomas of the endometrium than in carcinomas of the cervix, for which everyone would most likely resort to the well established and more dependable method of biopsy.

At that time my knowledge of the cytologic method was very limited and I was in no position to state whether a differential diagnosis between carcinomas of the cervix and adenocarcinomas of the fundus on a cytologic basis was possible. Nor did I know then that the diagnosis of carcinomas of the cervix by the smear method would be possible at an early asymptomatic stage, making it useful in detecting unsuspected lesions, which might still be invisible.

Now that the method has been tested by general use over a number of years our knowledge has been advanced to a point where we are able to differentiate with a fair degree of accuracy between lesions affecting different parts of the female genital tract, as well as between various cell types and smear patterns. We are now in a position to make a clearer distinction between the squamous cell type carcinomas of the cervix and the adenocarcinomas of the endometrium, in which the abnormal cells are of the glandular type. It is even possible at times to make a differentiation between an adenocarcinoma of the endometrium and one of the cervix, in which the abnormal cells are of the endocervical type.

Metaplasias of the endocervix and of the endometrium may also be recognized occasionally when clusters of endocervical or endometrial cells are present, in which some of the cells show a change toward the parabasal squamous type. In metaplasia of the endometrium one often encounters rosette-like clusters of cells in which there is marked enlargement and vacuolization of some of the more peripherally located cells. Endocervical or endometrial polypoid hyperplasias may be revealed by small polypoid fragments of the endocervical or endometrial mucosa found in endocervical or endometrial smears.

\* Presented as a Morning Lecture, Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 30, 1949.

The original work referred to in this paper has been aided by the Commonwealth Fund and by the National Cancer Institute.

From Cornell University Medical College.

The term "dyskaryosis" has been adopted to designate these early cytologic changes, which are centered in the nucleus. Several types of dyskaryosis may be distinguished on the basis of a predominance of one or more distinctive cell types.

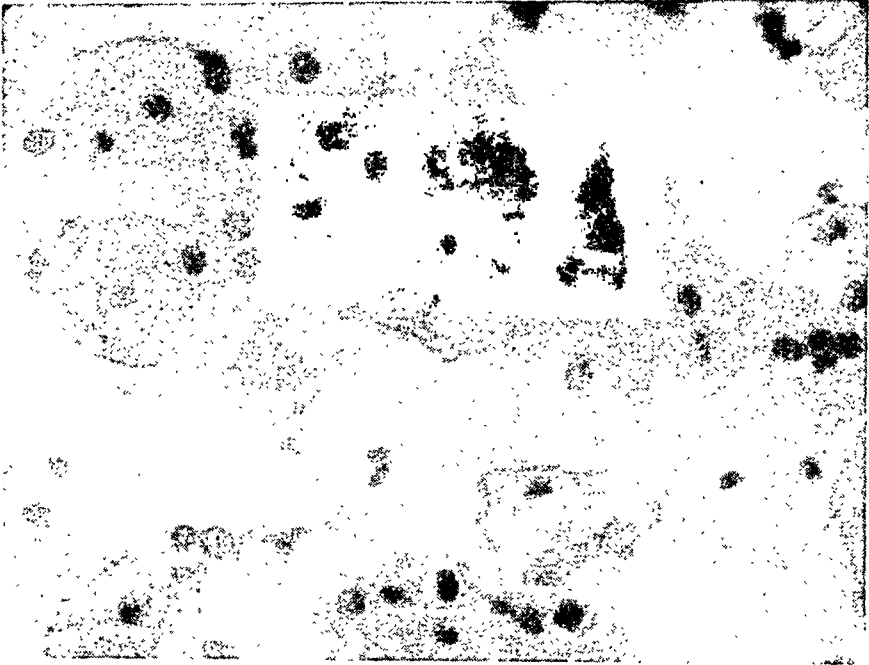


FIG. 1, *a*. Superficial squamous cells. Normal.  $\times 400$ .

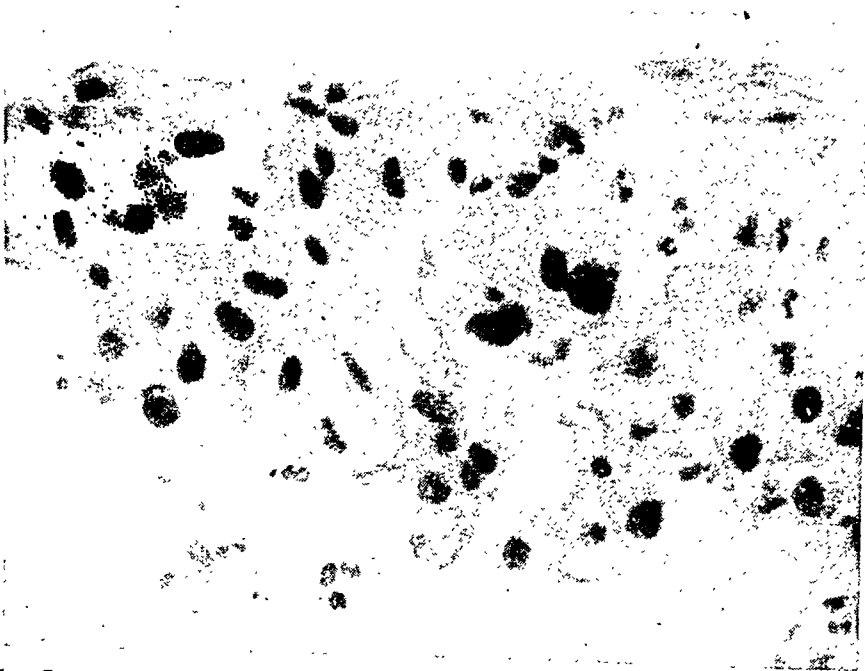


FIG. 1, *b*. Superficial squamous cells characteristic of superficial cell dyskaryosis.  $\times 400$ .

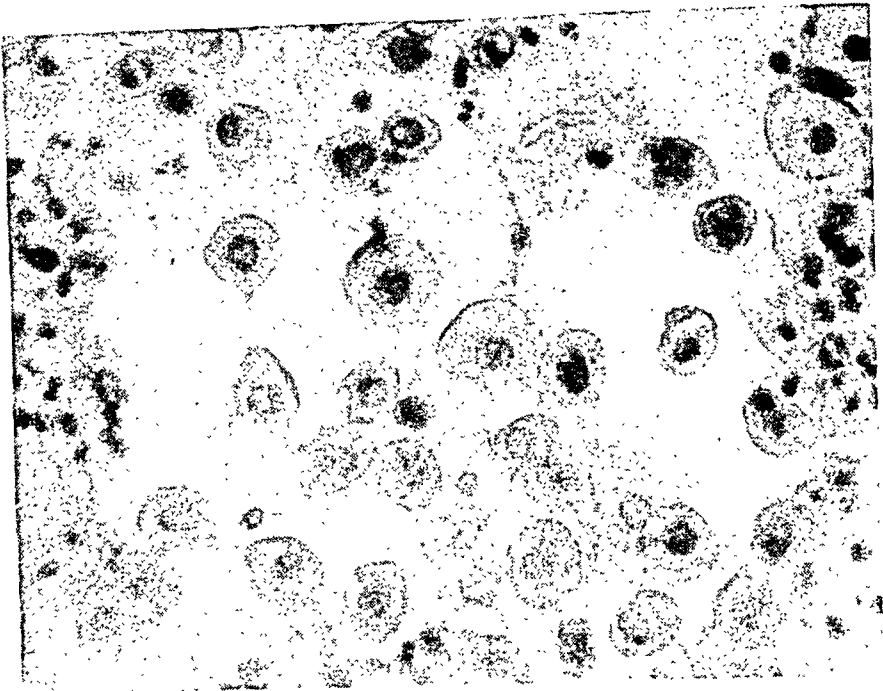


FIG. 3, *a*. Cervical parabasal cells. Normal.  $\times 400$ .

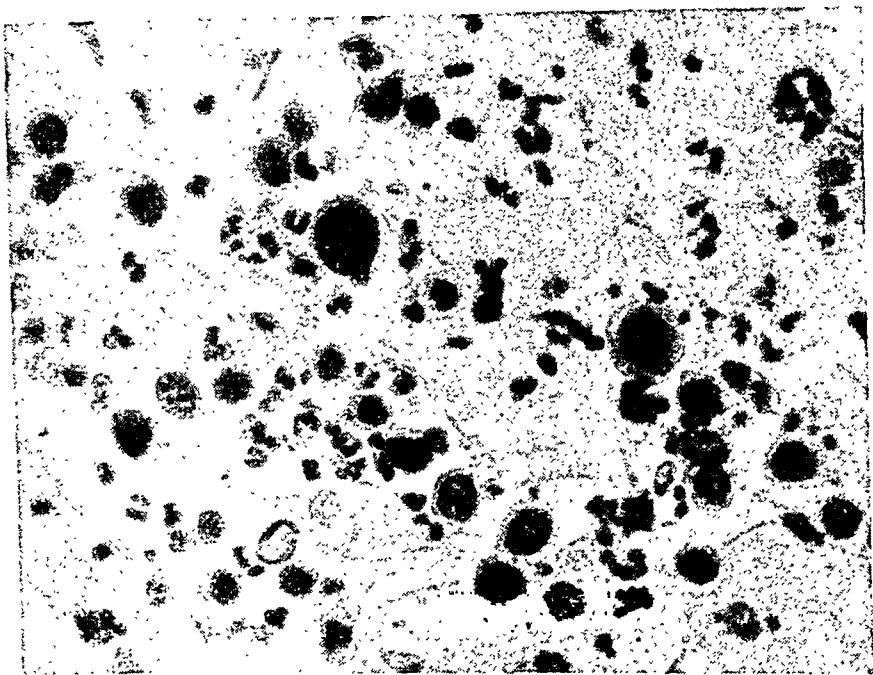


FIG. 3, *b*. Cervical parabasal cells characteristic of parabasal cell dyskaryosis.  $\times 400$ .

The term "intermediate or navicular cell dyskaryosis" is used to indicate the prevalence of abnormal cells deriving from the intermediate or navicular zone (figures 2a, 2b). This type of dyskaryosis is rather rare and thus far we have had only two clear-cut cases of it.

The significance and the prognostic value of these different patterns which seem to correspond to the earliest stages of malignant lesions of the cervix are not yet properly understood, nor will they be until an exhaustive correlative study of cytologic and pathologic findings has been made. What tends to complicate the picture is that not infrequently cells representing various dyskaryosis types are found to be intermixed.

Cases have also been noted in which the dyskaryotic cytology was found to coexist with that of an invasive squamous cell carcinoma. In some of these cases transitional cell forms linking the two cytologic patterns have also been observed. Should this fact be interpreted as indicating that the one would eventually develop into the other? An affirmative answer would be only an assumption, since in none of these cases have we had any positive evidence of a progressive change from one pattern to the other. On the other hand, in at least one case of superficial cell dyskaryosis, which we followed over a period of 10 years, this condition proved to be reversible.

Our observations in this field of early malignant lesions of the cervix and of their corresponding cytologic patterns are still fragmentary. It is not always possible to obtain a confirmation of smear findings by biopsy. Instances are not uncommon in which multiple biopsies have been necessary to prove the presence of an early carcinoma. In a recent case, only one out of eight biopsies taken offered positive evidence of a carcinoma in situ. Even after complete hysterectomy it is not possible to verify the absence of a malignant lesion without a serial microscopic study of the cervix, which is impracticable as a routine procedure.

Another difficulty is the lack of general agreement among pathologists as to the criteria of a carcinoma in situ. It sometimes happens that a section showing a marked degree of epidermidalization may be interpreted in some laboratories as carcinoma in situ. All these reasons make it very difficult to evaluate accurately the incidence of carcinoma in cases in which a dyskaryosis smear pattern has been observed.

In view of the fact that at present no general agreement can be reached as to the criteria of carcinomas in situ, their separation into two groups appears to be justifiable. One of the two groups would include cases characterized by clean-cut criteria that would be generally acceptable and that would satisfy the most exacting standards; the other would consist of cases in which the criteria fall below such standards and in which there may be disagreement as to the true nature of the lesion.

The term "carcinoma in situ" or "intraepithelial carcinoma" should be retained for the first group, whereas the second one should be designated by a new term which would not necessarily suggest malignancy. The term "pre-cancerous", which has been used extensively for ambiguous lesions, would be rather objectionable, as it implies an inevitable malignant transformation. In a recent discussion of this point the term "dysplasia"\* was

\* This term was suggested by Dr. William B. Ober of the National Cancer Institute at Bethesda, Maryland.



of the malignant cells, their extreme hyperchromasia, the anisokaryosis and the scantiness of the cytoplasm.

Adenocarcinomas may be recognized as such when the cells are well preserved and reveal their glandular origin. Exfoliated cells of this type frequently show an eccentric position of the nucleus and vacuolization of the cytoplasm. The cells are often grouped in rosette-like clusters.

Malignant neoplasms of lymphoid origin, such as Hodgkin's disease or reticulum-cell sarcoma, also present a distinct cytologic picture. The cells appear, as a rule, singly, and although relatively small, they can be safely identified by the coarse granulation, hyperchromasia, and fragmentation of their nuclei. An excess of lymphocytes was observed in some cases of lymphatic leukemia. In general, it may be stated that large clusters of lymphocytic cells in sputum or bronchial washings appear to be almost invariably associated with malignant neoplasms.

Another group of neoplasms of the lungs which show good exfoliation and can be detected by the examination of sputum or bronchial washings is that of the alveolar cell carcinomas. A cytologic feature which may help in the recognition of this type is the not infrequent presence of multinucleated cells of a rather characteristic appearance.

Of the non-malignant conditions, one which may occasionally display a distinctive cytology is bronchiectasis. Clusters of atypical cells which are sometimes found in this condition show considerable resemblance to clusters of neoplastic cells. The normal structure and the uniformity of their nuclei are a help in interpreting them correctly.

In our laboratory we attribute equal importance to the examination of sputum and to that of bronchial aspirates and washings. We have had instances of positive cases in which the sputum was negative and the bronchial washing positive, but other cases in which the contrary was true. When findings are negative at least three specimens should be examined.

In order to secure a good preservation of the cells we fix the sputum specimens in 70 per cent alcohol as soon as collected. The bronchial washings are mixed immediately with 95 per cent alcohol and then centrifuged. Smears prepared from the sputum, as well as those prepared from the sediment of the bronchial washings, are fixed again in alcohol-ether and stained by our standard smear-staining procedure which insures a good differentiation between basophilic and acidophilic cells. This differentiation is most important for the detection of the acidophilic and orangeophilic cells which are a characteristic feature of the squamous cell carcinomas.

In the urinary tract the most successful application has been in carcinomas of the bladder. As a rule, carcinomas of this organ exfoliate copiously and the cells usually appear in clusters showing structural abnormalities which reveal their malignant nature. In two instances an unsuspected carcinoma, concealed in a diverticulum of the bladder, has been detected by the use of the smear technic.

very scanty. The specific cytology of various types of tumors of the kidney still needs further clarification. Special methods of staining may eventually be found to be necessary for the identification of some of these types.

The administration of estrogens causes marked changes in the epithelium of some of the organs of the urinary tract. As a rule, these changes are reflected in the smears.- Both the transitional epithelium of the bladder and the glandular epithelium of the prostate may show cellular and nuclear enlargement and an increased production of glycogen as the result of a prolonged estrogenic therapy. Some of the superficial transitional cells change to a type resembling that of the cornified small-nucleated acidophilic squamous cells found in the vaginal secretion.

It is of interest that a prolonged administration of estrogens in prostatic carcinomas may cause an enlargement not only of the normal but also of the cancer cells, thus greatly facilitating their recognition in the smears. It is, therefore, likely that the use of estrogen therapy prior to the smear examination will tend to increase exfoliation and to cause cytologic changes that would help in the identification of exfoliated cancer cells. Such a use of estrogens has been proved to be of value in carcinomas of the female genital organs.

With regard to the matter of obtaining suitable urine specimens it may be stated in general that catheterized specimens are preferable to voided, more necessarily in women because of the admixture of vaginal cells in voided urine. The types of urine specimens required for the diagnosis of lesions of the prostate or of the ureter and kidney have already been mentioned.

The urine is mixed with an equal amount of 95 per cent alcohol as soon as collected.\* It is subsequently centrifuged, and smears prepared from the sediment are fixed again in an alcohol-ether solution and then stained by the same method used for other smears.

Special difficulties are encountered in the use of the smear method for the diagnosis of gastric carcinomas. Of these the two most important are the relatively rapid deterioration of exfoliated cells in the gastric fluid and the continual emptying of the gastric contents into the intestines, which does not allow a sufficiently large accumulation of exfoliated cells within the stomach. Another adverse factor is the rather frequent presence of extraneous cells in the gastric fluid. Clusters of cells from the nasal and bronchial mucosa and dust cells are those apt to be the most troublesome.

Despite these drawbacks the cytologic method is of recognized value in the diagnosis of gastric carcinomas. By improving our cytologic criteria and our technical procedures we hope to bring this application up to much higher standards, although the percentage of false negatives will most likely remain higher in this than in other applications.

\* The procedure of fixing specimens immediately and prior to centrifugation by mixing them with equal amounts of 95 per cent alcohol applies to all fluids with the exception of pleural and peritoneal fluids. These are mixed with equal amounts of 50 per cent alcohol, as the 95 per cent alcohol causes a much greater coagulation of proteins, which tends to reduce the amount of sediment.

As far as actual results are concerned it may be safely stated that certain applications, such as those of the female genital tract and of the respiratory tract, have been advanced to a point where they can now be used in routine laboratory diagnosis. There is an increasing number of publications dealing with the practical advantages and disadvantages of the method and giving an estimate of its dependability as a diagnostic procedure. Although the results obtained by investigators in different laboratories are at variance in some respects, they do permit one to arrive at certain conclusions, in which there is more or less general agreement.

One important point on which there is evidence of such an agreement is that the cytologic method is not to be considered as a method of final diagnosis and that confirmation of smear findings by biopsy or curettage is indicated wherever possible.

On the other hand, it is generally conceded, even by those who are most skeptically inclined, that this method is of unquestionable value in the detection of early or unsuspected carcinomas of certain organs, and is, therefore, particularly adapted to screening purposes. It is also highly useful in evaluating the effects and in following up the results of irradiation or other therapy.

With regard to the diagnostic accuracy of the method, it would be very difficult to make an overall statistical evaluation which would apply to all groups. Figures given out by various investigators show considerable variation. What we are striving for in our laboratory is to limit to a minimum the percentage of false positives. We feel that an accuracy of over 95 per cent can and should be maintained in the cases reported as Class IV and of over 98 per cent in those reported as Class V.\* Anything below these figures would not be at all satisfactory, more particularly in the Class V group, in which reports are often used as the basis of a decision for a major operation. Negative reports, as a rule, show a higher percentage of errors, ranging from 5 or 10 per cent, in well explored gynecological cases, to 25 per cent or even more in other applications, more specifically in the gastric.

Some of the drawbacks of the cytologic method are that it is time consuming and that it requires special study even on the part of men with a good pathological background. These disadvantages constitute a serious obstacle to the incorporation of the method in many laboratories and will, no doubt, greatly retard its more widespread adoption. What is more discouraging is the fact that in some laboratories, because of an increasing demand, the method is introduced prematurely, and is put into practice by men who have

\* Classification of reports on smears as applied to the diagnosis of malignant neoplasms

Class		
I	Negative	Absence of atypical or abnormal cells
II	Negative	Atypical cells present but without abnormal features
III	Suspicious	Cells with abnormal features suggestive of but not conclusive for malignancy
IV	Positive	Cells and cell clusters fairly conclusive for malignancy
V	Positive	Cells and cell clusters conclusive for malignancy

# CASE REPORTS

---

## ELECTROCARDIOGRAPHIC CHANGES IN A CASE OF WERNICKE'S SYNDROME \*

By LEON WALLACE, M.D., *Beverly Hills, California*, and  
EUGENE CLARK, M.D., *New York, N. Y.*

It is well known that the heart may be involved and that electrocardiographic changes are found in conditions due to deficiency of the vitamin B complex. This has been shown to occur in beriberi and pellagra.<sup>1, 2, 3, 4, 5, 6, 7, 8</sup> The following case is of interest because of the occult cardiac involvement with striking electrocardiographic abnormalities, which disappeared rapidly after thiamine chloride therapy, in a patient with Wernicke's syndrome (hemorrhagic polioencephalitis superior), a state which clinical and experimental evidence holds ascribable to thiamine deficiency.<sup>9, 10, 11, 12</sup>

### CASE REPORT

A 40 year old white man entered the hospital in a confused state. He was disoriented as to time and place, confabulated, and frequently contradictory. The only history which appeared to be reliable was the admission of chronic alcoholism for at least six years, accompanied by a grossly inadequate food intake. Diplopia of 24 hours' duration was admitted to be present; headache was denied. A questionable history of peptic ulcer was given. No history of heart disease was obtained.

At the time of admission the following physical findings were present: Temperature 99.2° F., pulse 150, respirations 20, blood pressure 114 mm. Hg systolic and 80 mm. diastolic.

The head showed no evidence of injury. The pupils reacted to light and accommodation, and were round, regular and equal. There was left external rectus palsy with diplopia; horizontal, but no vertical nystagmus. The fundi were normal. The ears, nose, mouth, throat and neck were essentially normal.

The lungs were clear to auscultation and percussion. The heart was not enlarged. The sounds were of good quality and regular. Sinus tachycardia was present. There were no murmurs or thrills.

The abdomen was flat and slightly tender in the right upper quadrant. The kidney, spleen and liver were not palpable. Genitalia were normal. The extremities revealed slight cyanosis of both feet and hands.

*Neurological examination:* Deep tendon reflexes were normal in the upper extremities, absent in the lower extremities. The Babinski reaction was equivocal, and plantar hyperesthesia was present.

*Laboratory findings:* White blood count 4850; neutrophils 60 per cent, lymphocytes 33 per cent, mononuclears 2 per cent, eosinophiles 2 per cent, basophiles 3 per cent. Red blood count 4,870,000; hemoglobin 14.5 gm. The Wassermann reaction was negative. Sodium: 312 mg./100 c.c. Non-protein nitrogen: 32 mg./100 c.c.

\* Received for publication November 15, 1946.

From the Third (New York University) Medical Division of Bellevue Hospital, and the Department of Medicine of the New York University College of Medicine.

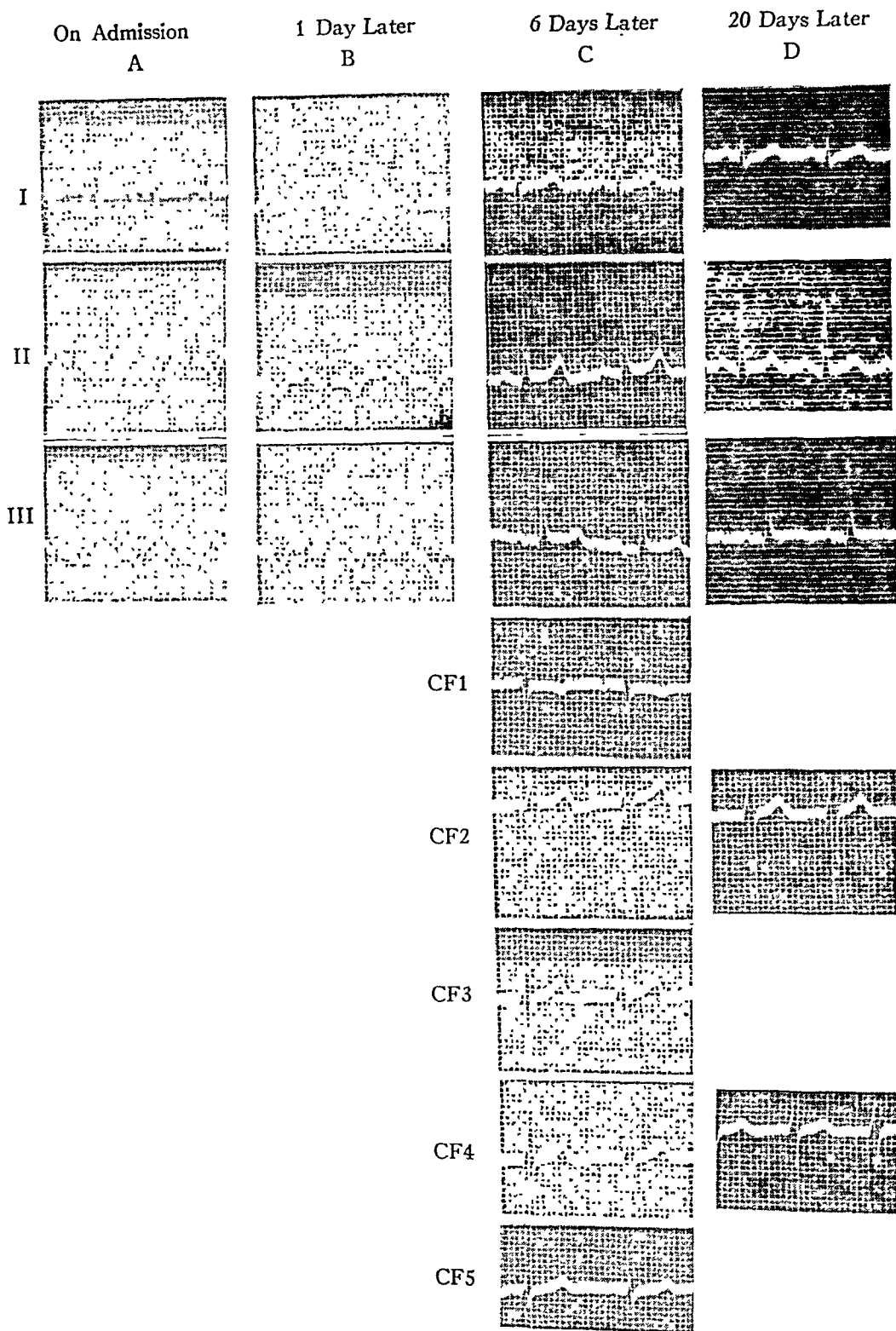


FIG. 1. *A.* On day of admission. Sinus tachycardia of 140. The abnormalities are the low T in Lead I and the inverted T in Leads II and III. *B.* One day later. Sinus tachycardia of 107. The low T in Lead I and the inverted T in Leads II and III persist. *C.* Six days later. Sinus rhythm of 83. The abnormal T waves are now normal as is the entire record. *D.* Twenty days later. Sinus tachycardia of 107. Normal record. The timer was not working while the first three leads were taken.

edge, has as yet appeared in the literature concerning its use in acute infectious mononucleosis. Because of the highly favorable results obtained with it in some viral diseases, it was deemed advisable to try aureomycin \* in a patient with this disease.

#### CASE REPORT

A white female, age 17, became ill on December 29, 1948 with malaise and slight fever. On the following day, she developed a sore throat and when she was first seen at her home on December 31, her temperature was 102° F. Examination at that time revealed the presence of a yellowish-white exudate on both faucial tonsillar stubs as well as on discrete lymphoid tissue deposits on each postero-lateral pharyngeal wall. The exudate assumed a follicular distribution. On either side of the neck, below the angle of the mandible, a solitary lymph node was enlarged and tender but no other lymph glands were palpable. She was given 300,000 units of penicillin in oil intramuscularly that day and on each of the next five days, a total of 1,800,000 units, without any beneficial effect on the course of the illness. Her temperature continued, fluctuating between 100.5° F. and 102° F. until January 4, 1949 and between 102° F. and 104.5° F. until January 7. The exudate, originally in a follicular pattern, now assumed a membranous appearance, involving not only the original sites, but the base of the tongue and the hypopharynx as well. The nasopharynx could not be seen but the clinical condition suggested involvement there, too. She developed a moderate cough with pain in the upper retro-sternal region. On January 5, the eighth day of the disease, the spleen was palpable. The submaxillary glands originally involved remained unchanged but a posterior cervical gland on either side became enlarged and tender. The patient was obviously quite toxic.

A blood count on the seventh day of illness revealed: hemoglobin, 16.7 gm. (104 per cent); red blood cells, 5,100,000; white blood cells, 9200 with a differential count of 33 per cent polymorphonuclear neutrophils, 65 per cent small lymphocytes and 2 per cent monocytes. The serum of blood taken the same day for heterophile antibody determination gave a positive agglutination in a dilution of 1:1792. Two throat cultures during the first six days were sterile for the diphtheria bacillus, positive for *Staphylococcus aureus* and gram negative diplococci.

Aureomycin was started orally at 1 p.m. on the tenth day of the disease on the morning of which the temperature reached 104.5° F. One hour before therapy was begun, however, the temperature dropped to 102° F. After 2.75 gm. were administered during the first 24 hours, the temperature dropped to 98.8° F. (figure 1). She received 2 gm. during the next 24 hours, her temperature varying between 98.8° F. and 100.5° F. After having had 3.75 gm. she developed some nausea and, on one occasion, vomited. The nausea, of slight degree, persisted for about 36 hours when she had two loose bowel movements. The dose for the third day, therefore, was reduced to 1.5 gm., a similar dose being given on the fourth day. The temperature assumed a normal level on the third day, there being no subsequent rise. A final dose of 1 gm. was given on the fifth day, making a total of 8.75 gm.

Twenty-four hours after treatment was begun, the patient no longer appeared toxic although she still had considerable dysphagia; the cough and retro-sternal distress disappeared; the spleen was no longer palpable; the enlargement and tenderness of the cervical glands were unequivocally less, reaching a normal state 96 hours after therapy was started. No other glands became palpable. There was no change in the pharyngeal exudate until 48 hours after the drug was begun, at which time several of the lesions began to shrink at their periphery and the dysphagia was minimal. Three days later, the throat was entirely clear.

\* Aureomycin was obtained through the courtesy of Lederle Laboratories Division, American Cyanamid Company.

case reported here might well fit into that category and it may well be that the normal course of this patient's illness would have been prolonged. In this case, it is noteworthy that, coincident with the use of aureomycin, the following changes in the clinical course of the disease occurred within 24 hours:

1. A significant drop in temperature.
2. The spleen was no longer palpable.
3. The patient became markedly less toxic.
4. There was definite diminution in the swelling and tenderness of the cervical lymph nodes.

These observations warrant further clinical trial of aureomycin in infectious mononucleosis.

#### BIBLIOGRAPHY

1. DUGGAR, B. M.: Introductory paper, in Conference on Aureomycin—A New Antibiotic, New York Academy of Sciences, Section of Biology, July 21, 1948.
2. WONG, S. C., and COX, H. R.: Action of aureomycin against experimental rickettsial and viral infections, *Ann. N. Y. Acad. Sci.*, 1948, li, 290-303.
3. BRYER, M. S., SCHOENBACH, E. G., CHANDLER, C. A., BLISS, E. A., and LONG, P. H.: Aureomycin—experimental and clinical investigations, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 117-119.
4. FINLAND, M., COLLINS, H. S., and PAIN, T. F.: Aureomycin—a new antibiotic, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 946-949.
5. WRIGHT, L. T., SANDERS, M. S., LOGAN, M. A., PRIGOT, A., and HILL, L. M.: Aureomycin—a new antibiotic with virucidal properties, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 408-412.
6. SPINK, W. W., BRAUDE, A. I., CASTANEDA, M. R., and GOYTIA, R. S.: Aureomycin therapy in human brucellosis, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 1145-1148.
7. SCHOENBACH, E. B., BRYER, M. S., and LONG, P. H.: The pharmacology and clinical trial of aureomycin: a preliminary report, *Ann. N. Y. Acad. Sci.*, 1948, li, 267-279.
8. BRALEY, A. E., and SANDERS, M.: Aureomycin in ocular infections, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 426-427.
9. MCKINLEY, C. A., and DOWNEY, H.: *Oxford medicine (Christian)*, 1944, v, 498.

### HYPERTROPHIC OSTEOARTHROPATHY; REPORT OF A CASE ASSOCIATED WITH A CHORDOMA OF THE BASE OF THE SKULL AND LYMPHANGITIC PULMONARY METASTASES \*

By NATHANIEL UHR, Lt. Col., Medical Corps, A.U.S., F.A.C.P., and  
JACOB CHURG, Captain Medical Corps, A.U.S.,  
*Topeka, Kansas*

MUCH knowledge regarding the clinical aspects of hypertrophic osteoarthropathy has been acquired in the past half century. Its etiology and mechanism, however, remain to be elucidated. In the majority of cases, osteoarthropathy, with its concomitant clubbing of the fingers and toes, is seen as a sequel of chronic suppurative or neoplastic disease of the thoracic organs, less commonly

\* Received for publication May 31, 1946.

but the testicles were much smaller than usual. Studies of ocular fundi disclosed slight papilledema with tortuosity of the veins, more marked on the left. These changes became more pronounced on subsequent examinations. Neurological examination one week after admission revealed exaggerated patellar and Achilles tendon reflexes, the sign of Babinski on the right and a questionable response on the left. Position sense was absent on the right and impaired on the left. Diplopia was noted when the object was at the extreme left; this became progressively more marked within the next two weeks. Bronchoscopy was attempted, but could not be performed because of trismus.

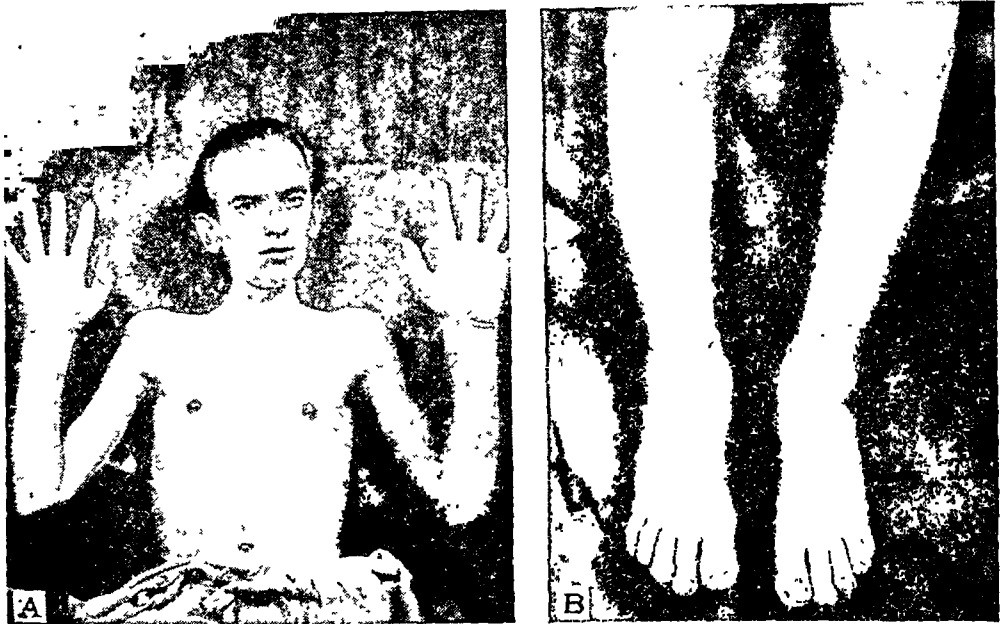


FIG. 1. *a* and *b*: Appearance of patient three weeks before death. Note thickening of forearms and legs.

The subsequent course in the hospital was dominated by increasing clinical and roentgenographic signs of pulmonary involvement. The patient developed cough with moderate expectoration. Rapidly increasing signs of infiltration of the right lung and pleural effusion were followed by similar involvement on the left. The periosteal changes became extremely marked (figure 2, *a* and *b*) and extended to the distal ends of the femora and humeri. Atrophy occurred about the joints. Roentgenograms of the skull revealed marked osteoporosis of the sella turcica with some erosion of the floor and the posterior clinoid processes (figure 2, *d*). The sedimentation rate was persistently elevated: up to 52 mm. per hour. The blood calcium was 11.7 mg. per cent, phosphorus 4.2 mg. per cent, alkaline phosphatase 5.9 Bodansky units; white blood count and differential were within normal limits; red blood count was between 4.0 and 3.6 million, with hemoglobin between 12 and 10.8 grams per cent. During the last few days before death fever increased, with irregular elevations up to 103° F. Progressive embarrassment of respiration with cyanosis occurred and was followed by coma and death on July 14, 1944, approximately six months after the onset of symptoms.

**Autopsy.** The autopsy was performed eight hours after death. Only pertinent findings are recorded.

**Gross Examination. Skull:** The bones of the skull cut with usual resistance. The meninges were smooth, the subarachnoid fluid clear and colorless and not increased in amount. The vessels of the brain were markedly injected. The base of the



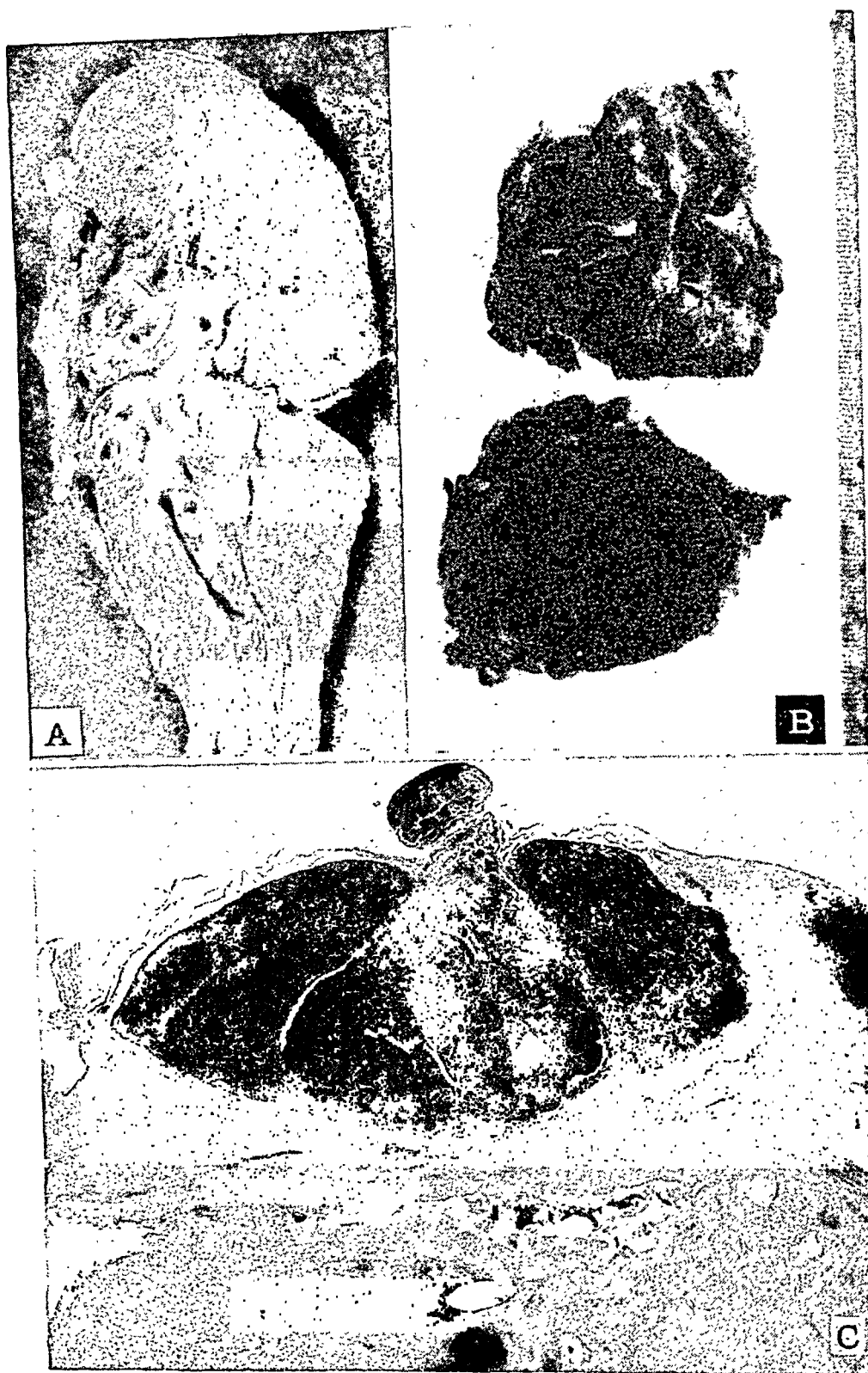


FIG. 3. *a*: Section of the right lung showing peribronchial and perivascular spread of the tumor. *b*: Tumor at the base of the skull and roof of the nasopharynx. *c*: Relation of the tumor to the pituitary gland. Note complete destruction of the sella turcica and the few remaining bony trabeculae within the tumor ( $\times 10$ ).

the gland were well preserved, the majority having distinctly eosinophilic cytoplasm. Along the periphery of the gland were several small areas of necrosis.

*Lungs:* Sections from various parts of the lungs showed a similar microscopic picture. The perivascular, peribronchial and subpleural lymphatics were markedly

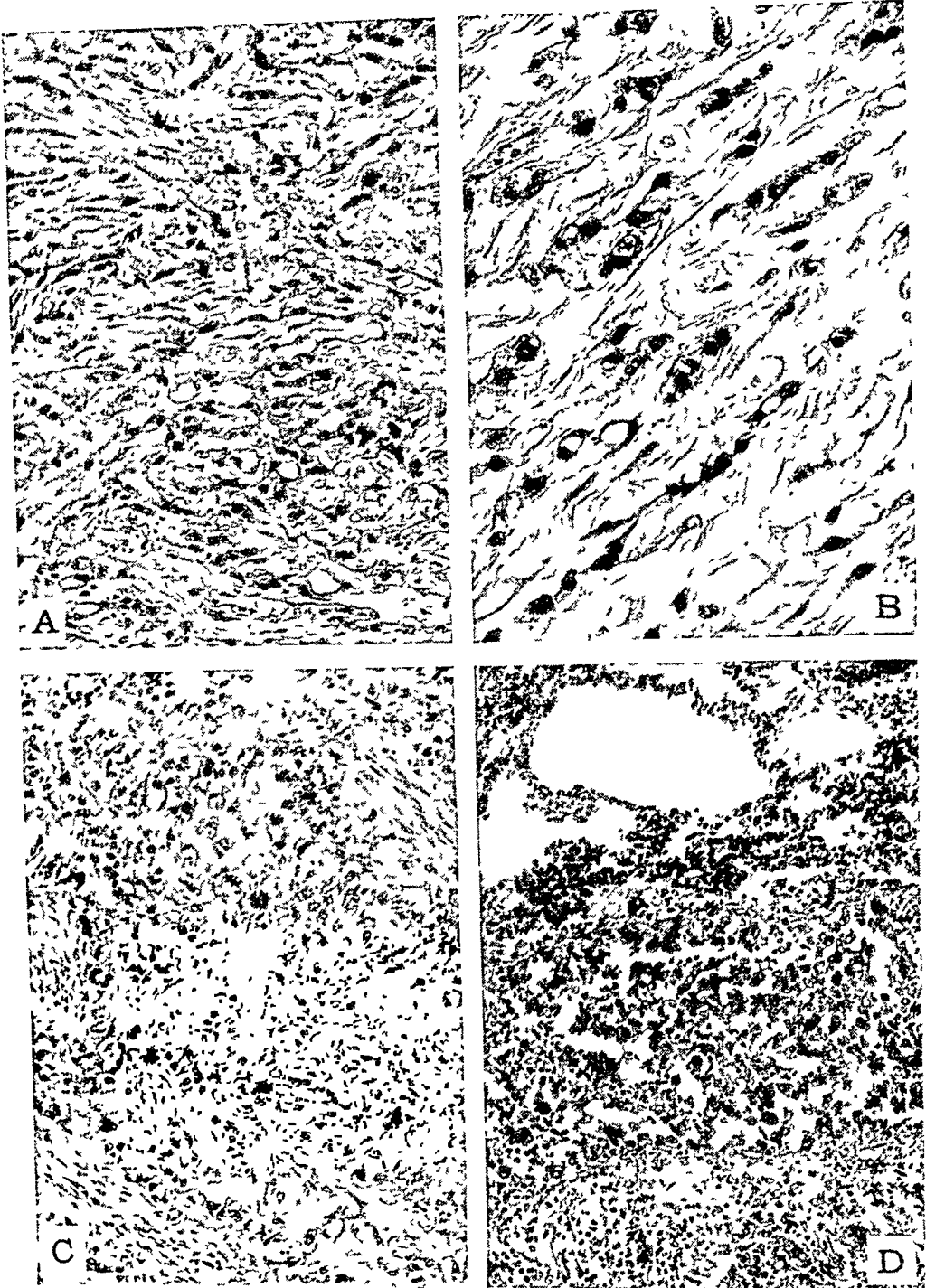


FIG. 4. *a* and *b*: Tumor at the base of the skull showing syncytial meshwork of elongated and stellate cells, "signet ring" cells and the faintly fibrillar, transparent intercellular substance (*A* —  $\times 180$ ; *B* —  $\times 350$ ). *c*: Tumor invading the roof of the nasopharynx. Variation in appearance of cells ( $\times 180$ ). *d*: Tumor cells in a pulmonary lymphatic ( $\times 160$ ).

clear leukocytes intermixed with the tumor cells. In some areas the neoplasm appeared to break out of the lymphatics and infiltrate the adjoining parenchyma and the walls of the smaller blood vessels and bronchi. At one point, in the right main bronchus, the tumor had actually reached the lumen. The parenchyma especially in the right lower lobe was compressed and atelectatic; many alveoli contained edema fluid and polymorphonuclear leukocytes; others were filled with tumor cells. Occasional small blood vessels were occluded by fibrin thrombi.

*Pleura:* The pleura was markedly thickened by masses of tumor tissue, reproducing the structure of the tumor in the base of the skull. Small areas of elongated cells mixed with considerable mucinous intercellular substance, alternated in an irregular fashion with large areas of dense ground substance containing nests of cuboidal cells arranged about small empty spaces. There was a fair number of "signet ring" cells and also many elongated cells resembling fibroblasts. Areas of necrosis were fairly numerous.

*Para-aortic lymph node:* The lymphoid tissue was almost completely replaced by the tumor exhibiting the same pattern as in the pleural metastases. Some of the sinusoids and many of the lymphatics in the immediate vicinity were filled by syncytial masses of cells as seen in the pulmonary lymphatics.

*Testis:* Tubules were well developed but showed incomplete spermatogenesis.

*Fibula:* The original structure of the bone was well preserved, though widening of many of the Haversian canals suggested resorption. The marrow cavity was filled with fat. Superimposed upon the original cortex was a thick irregular meshwork of newly formed trabeculae, covered by thickened periosteum (figure 5, b). The intertrabecular spaces were filled with loose connective or fatty tissue containing occasional clumps of small round cells.

### COMMENT

The autopsy confirmed the clinical impression of extensive neoplastic involvement of the lungs, and massive hypertrophic osteoarthropathy. The changes at the base of the skull were caused by a malignant tumor identical in structure with that found in the chest. The involvement of the lungs was of "lymphangitic" variety with only secondary infiltration of the parenchyma, bronchial walls and blood vessels. There was no particular area which could have been designated as the primary focus. This fact argued against primary pulmonary neoplasm with metastases to the base of the skull. Reconsideration of the clinical course and detailed histological studies led us to believe that the converse, in fact, was true, that the tumor originated within the base of the skull and metastasized to the lungs and pleura.

The microscopic structure was characterized by the presence of fairly large elongated and polygonal cells with varying amounts of eosinophilic cytoplasm, often containing large vacuoles, and by abundance, in some areas, of clear intercellular mucinous substance. Though the typical "physaliferous" cells are missing, the polymorphous appearance with syncytial-like structure, vacuolization of the cytoplasm, accumulation of intercellular mucinous substance and tendency to arrangement around clear spaces, strongly suggest the diagnosis of chordoma. The topography of the tumor, the location of the most differentiated areas beneath the sella turcica, and the expansion of the involved bones testifies to the intraosseous origin of the growth. These features also help to exclude other tumors at the base of the skull, such as lympho-epithelioma and transitional cell carcinoma of the nasopharynx or sphenoid sinuses. The subsellar, intrasphenoid

of pulmonary neoplasm with hypertrophic osteoarthropathy, emphasized the similarity of certain aspects of this condition to acromegaly, and suggested dyspituitarism as a probable cause. This hypothesis was supported in his cases by acromegalic features, atrophy of testes and gynecomastia in the male, hirsutism and secondary male characteristics in the female, and also by hyperplasia of eosinophilic elements in the pituitary gland. In our case, except possibly for testicular atrophy, no evidence of endocrine dysfunction was observed, yet the pituitary gland showed distinct increase of eosinophilic cells in areas not involved by the tumor. More clinical observations and pathological data are required to establish the rôle of the endocrine apparatus and particularly the pituitary gland in hypertrophic osteoarthropathy. Until then, this theory must be considered an interesting but unproved possibility.

### SUMMARY

1. A case of chordoma at the base of the skull is reported.
2. It is characterized by a high degree of malignancy, unusual for chordoma, by lymphangitic pulmonary metastases, and by early and massive hypertrophic osteoarthropathy.

We offer grateful acknowledgment for the assistance and suggestions given by Drs. S. B. Wolbach and Thomas D. Kinney and Dr. Sadao Otani.

### BIBLIOGRAPHY

1. FAUST, D. B., GILMORE, H. R., JR., and MUDGETT, C. S.: Chordomata: a review of literature, with report of a sacrococcygeal case, *Ann. Int. Med.*, 1944, xxi, 678-698.
2. BRUCE, J., and MEKIE, R.: Chordoma, *Surg., Gynec. and Obst.*, 1937, lv, 40-47.
3. MENDLOWITZ, M.: Clubbing and hypertrophic osteoarthropathy, *Medicine*, 1942, xxi, 269-306.
4. MARIE, P.: De l'ostéo-arthropathie hypertrophiante pneumique, *Rev. de méd.*, 1890, x, 1-36.
5. BAMBERGER, E. VON: Ueber Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten, *Ztschr. f. klin. Med.*, 1890, xviii, 193-217.
6. FRIED, B. M.: Chronic pulmonary osteoarthropathy. Dyspituitarism as probable cause, *Arch. Int. Med.*, 1943, lxxii, 565-580.

## A CASE OF A PUTRID EMPYEMA WITH A BRONCHO- PLEURAL FISTULA SUCCESSFULLY TREATED WITH PENICILLIN \*

By ARTHUR L. FORSGREN, M.D., *Minneapolis, Minnesota*

RAPID advances have been made in the treatment of empyema thoracis with the advent of penicillin, especially with its use intrapleurally. In all probability,

\* Received for publication March 24, 1947.

From Veterans Administration Hospital, Minneapolis, Minnesota, and the Department of Medicine, University of Minnesota.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

and a broncho-pleural fistula, the patient made a surprisingly prompt and uneventful recovery under intensive penicillin therapy. The patient received intramuscular penicillin, penicillin aerosol, and intrapleural instillations of penicillin.

The concomitant existence of a broncho-pleural fistula, in the cases of putrid empyemas successfully treated medically, demonstrates that such a fistula can

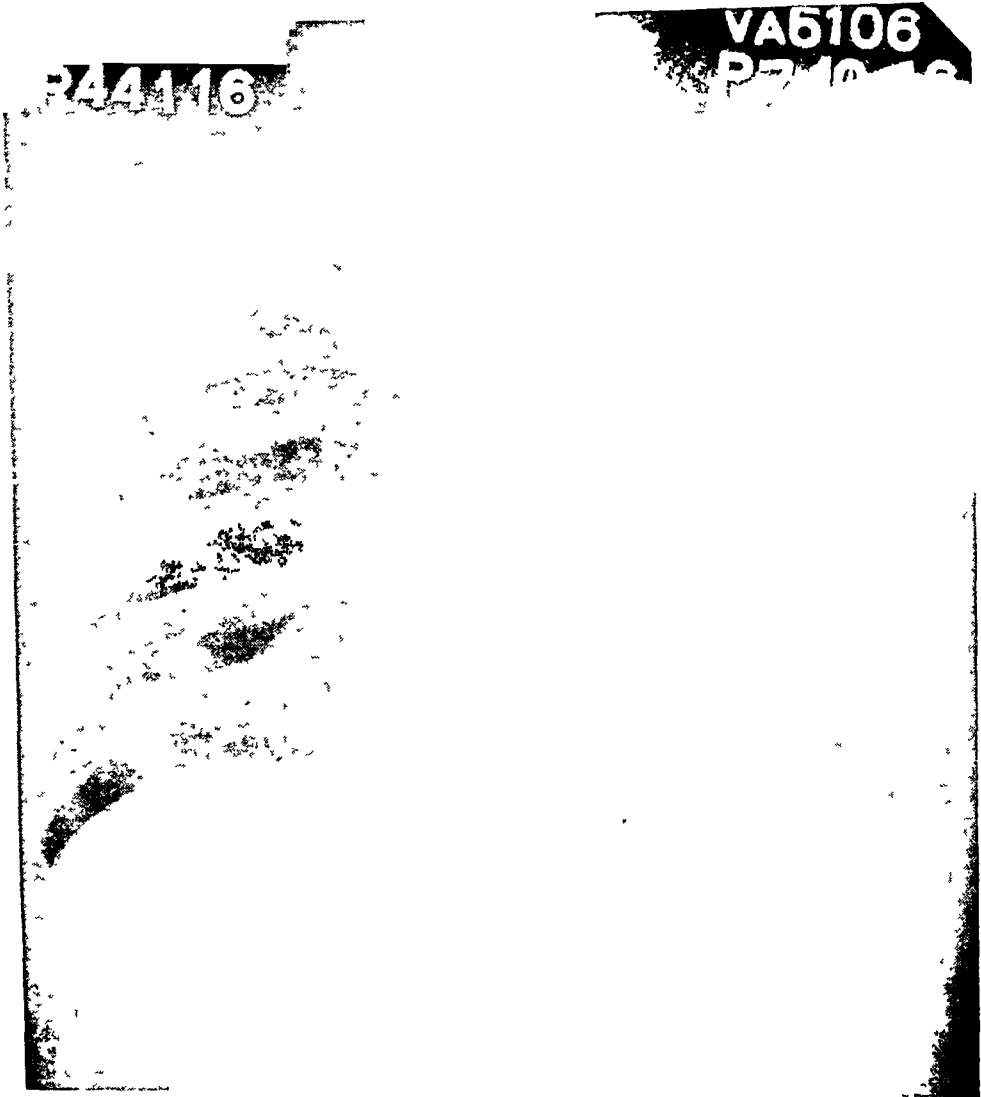


FIG. 2. During therapy.

heal without open drainage if the infection can be controlled. It also suggests that the fistula might have served a useful purpose in emptying the empyema cavity.

#### CASE REPORT

A 52 year old farmer first became ill during the last week of May, 1946. At this time he noted a sudden onset of chills and fever subsequent to the extraction of three abscessed teeth. The following day he had severe, anterior left chest pain on

were carious and moderately advanced pyorrhea was present. There was mucopurulent material in the pharynx. No cardiac abnormalities were noted; no organs or masses were palpable in the abdomen.

Examination of the chest revealed slight atrophy of the muscles over the left chest. The right lung was normal to auscultation and percussion. There was resonance over the left anterior lung, in the left axilla, and over the extreme upper portion of the left posterior lung. The lower three-fourths of the left posterior lung revealed dullness to flatness on percussion; tactile fremitus was decreased over this

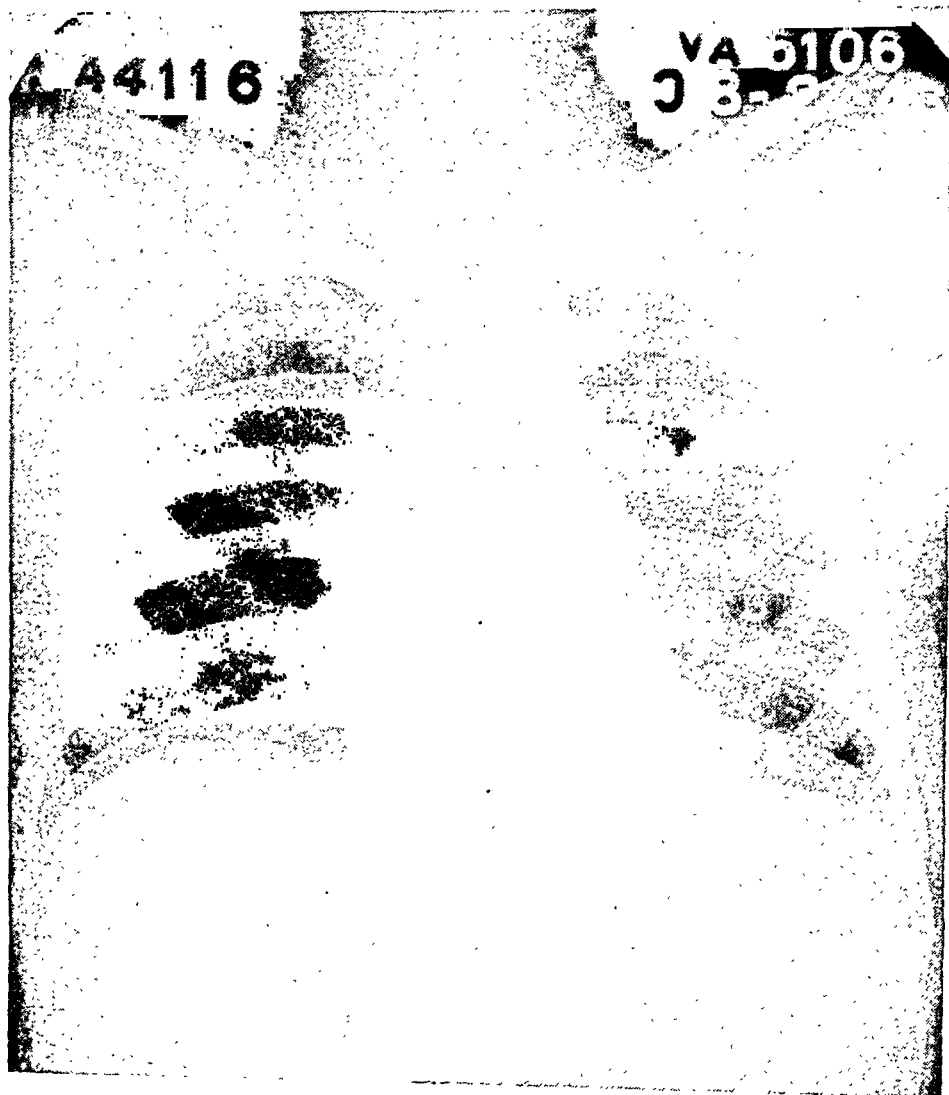


FIG. 4. After therapy.

area and the breath sounds were diminished though bronchial in quality. The sputum was green, purulent, and odorless.

Laboratory studies on admission showed the hemoglobin to be 11.8 gm., with 3,680,000 red blood cells. White count was 14,400, with 82 per cent neutrophils, 15 per cent lymphocytes, and 3 per cent monocytes. Urinalysis showed a specific gravity of 1.015, with albumin and sugar negative. Postero-anterior chest roentgen-ray showed a density involving almost the entire left chest with an airfluid level in

After four penicillin instillations there was marked clinical improvement. Surgical intervention was not considered necessary. Chest roentgenograms showed marked diminution in the size of the cavity and in the amount of fluid. No fluid was obtained on thoracentesis. Intramuscular and nebulized penicillin was continued for two weeks, during which time the patient became asymptomatic and afebrile, the cough disappeared, and the white blood count fell to 7,500. The vital capacity increased to 2.9 liters. On August 1 all penicillin was discontinued. Chest roentgen-ray showed evidence of thickened pleura, as did physical examination, but no encapsulated fluid could be visualized. At this time the patient had gained 15 pounds since admission. The patient was discharged from the hospital on August 9, eight days after discontinuation of penicillin, no symptoms, febrile reaction, or positive physical findings having recurred.

The total period of hospitalization following diagnostic thoracentesis was four and one-half weeks.

Fifteen weeks after discharge from the hospital the patient was entirely asymptomatic and engaged in his normal farming activities:

### CONCLUSION

A case is presented demonstrating the cure of a putrid empyema with a broncho-pleural fistula obtained with penicillin therapy.

### BIBLIOGRAPHY

1. BROWN, BRUCE, ORY, EDWIN M., MEADS, MANSON, and FINLAND, MAXWELL: Penicillin treatment of empyema: report of 24 cases and review of the literature, *Ann. Int. Med.*, 1946, xxiv, 343-370.

organization of the pattern with loss of the regular sequences of rhythmic waves. The amplitude may be increased or diminished. There may be bilateral asymmetry, either in frequency or amplitude, of the waves. There may be "slow" waves (less than 8 per second), either isolated "random" waves, focal or diffusely scattered over the head; or such waves may come in regular sequences which are of great significance, especially if their amplitude is high. "Spikes" may occur, similarly distributed, brief, sharp-tipped waves, often of high amplitude.

Finally there is the well known "wave-and-spike" or "spike-and-dome" pattern, usually occurring in regular rhythmic series and generalized. This is always found during a clinical petit mal seizure, is often present in such cases in intervals between clinical seizures, and occurs occasionally between seizures in patients with convulsive attacks in whom no clinical petit mal seizures have been recognized. Although virtually pathognomonic of idiopathic epilepsy, this pattern has been reported as a sequel of encephalitis in children.

The first major application of the EEG to clinical diagnosis and perhaps the most important was in epilepsy, following the observations of Lennox and Gibbs. Immediately preceding a grand mal seizure highly characteristic changes occur, consisting often of numerous spikes associated with and eventually replaced by a generalized sequence of rhythmic slow waves of high amplitude. In the interval between seizures in some cases there are occasional short sequences ("bursts") of spikes, rhythmic slow waves, or both. Quite frequently there are only random scattered slow waves which are abnormal but not in themselves diagnostic, and in about 15 per cent of the cases no clear cut abnormality can be found.

The wave-and-spike pattern of the petit mal seizures has been noted. In "psychomotor epilepsy," episodes of abnormal behavior regarded by some as an "epileptic equivalent," Gibbs has described slow, notched or flat-topped waves, but others have questioned their significance as a manifestation of epilepsy.

Finally there is a group of clinically normal individuals, according to some constituting up to 15 per cent of the population, whose records show non-specific abnormalities, usually of minor degree.

Focal destructive lesions involving the cortex, including tumors, abscesses, local traumatic lesions, subdural hematoma and scars resulting from such lesions, cause definite abnormalities in many cases. The commonest manifestation of superficial cortical lesions is the occurrence of random slow waves, generally not equal or rhythmic, which are usually localized. More rarely there may be spikes alone or a mixture of spikes and slow waves, but only if the electrode is close to the tumor. There may be a similar disturbance in the symmetrical area on the other side but usually of lower amplitude. The abnormal waves do not arise from the tumor, which electrically is relatively "dead" tissue, but from the damaged cortex at the margin of the tumor. In the case of deep tumors the disturbance may be generalized.



As already noted, normal records are obtained in a significant percentage of patients with epilepsy or organic brain disease. Various procedures have been tried to elicit abnormalities in such cases, of which hyperventilation is the most useful and is now practically a routine procedure. Even in normal individuals, however, and particularly in children it tends to cause disorganization of the pattern and slowing of the activity, and care must be used in the interpretation. Injections of metrazol have been used, but the technic has not been adequately standardized.

Sleep or drowsiness causes marked changes in the EEG, depending upon the depth of sleep. The most important are a general slowing of the rate and the appearance of irregularly distributed slow waves of high amplitude which may be interpreted by the unwary as indications of disease. There is also a fast component, sequences of waves at 12 to 14 per second that often appear in the form of "spindles."

Records taken during sleep often yield information not obtained in waking records, particularly if they include shifts between the waking and sleeping state. Sleep may be natural or induced by hypnotics, of which seconal seems at present to be the most satisfactory. The characteristic changes in epilepsy may often be induced in this way; these are not masked by sleep, but they can be more easily recognized. Sleep markedly lessens the artefacts in the records due to gross muscular movement or tension, and it may be the only way of obtaining records in hyperkinetic or unruly children.

To be of value it is essential that the test be carried out with meticulous care by a thoroughly trained technician. The requirements in this respect are far more exacting than for any of the other diagnostic procedures in common use. Artefacts arising from technical errors or mechanical defects in the apparatus may simulate almost any of the pathological alterations that have been described. Particularly disturbing are spikes and waves of increased amplitude, either scattered or in sequence. Among the commoner sources of trouble are poorly applied or loosened electrodes, improperly placed electrodes, spread of electrode paste, sweating, swaying of the electrode wires, restless movements of the patient, blinking of the eyes, unrecognized drowsiness, faulty or "noisy" vacuum tubes and static electrical disturbances arising from sparking motors, diathermy or roentgen-ray machines. Tension or twitching of the cranial muscles, especially the temporals, causes "muscle spikes" which may obliterate other features of the tracing or, if sparse, may be mistaken for spikes of cortical origin.

The individual who interprets the record must be familiar with these artefacts and differentiate them from significant alterations. This is not always easy. He must be familiar with the standards of normal, which vary with age. In normal infants the records are poorly organized and show predominantly irregular slow activity. The shift to the adult pattern is gradual and is not usually attained until the fourteenth to eighteenth year. The record of any normal child is, therefore, likely to show aberrations from the adult pattern which would be pathological in an older age group.

## REVIEWS

*Clinical Allergy.* By LOUIS TUFT, M.D., Assistant Professor of Medicine, Temple University School of Medicine; Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital, Philadelphia, Pennsylvania. Second edition. 690 pages; 16 × 24 cm. Lea and Febiger, Philadelphia 6, Pennsylvania. 1949. Price, \$12.00.

In the opinion of this reviewer, Dr. Tuft's book is the best text on allergy available. The present volume is planned along lines similar to those followed in his original, or previous edition. However, it has been thoroughly rewritten and is modern in every sense. The volume is attractive in appearance, is a reasonable size, the type is clear, and the subject matter well arranged.

The author has retained his basic method of presentation in that the major divisions of the text are unchanged. First, general considerations of allergy are presented with a satisfactory discussion of the basic facts of anaphylaxis and allergy. This serves as an adequate orientation for the uninitiated and, in addition, will bring the practicing allergist abreast of current thinking about important phases of these subjects. The author then discusses etiological agents in groups, pointing out the important group characteristics of different types of allergens and calling attention to the clinical significance of these facts.

His discussion of the clinical manifestations of allergy, that is, the conditions one must treat practically, is sound, complete, and sufficiently free from confusing speculation to make it of great value in the clinical application of the vast amount of data his book contains.

In his discussion of the treatment of asthma, those of us who have used Butanefrine extensively will be disappointed to find no mention of this very valuable drug; particularly, when one considers the space given to other agents of doubtful value, some of which he condemns. This omission is difficult to understand.

This volume is a textbook in the best sense of the word. It is sufficiently dogmatic to permit the reader to chart a course clinically. Pertinent facts are given, doubtful data have been omitted. The author, also, avoids the temptation to coin new phrases and to add new classifications to the multiplicity of these now extant that dog the beginner in his attempt to see different phases of allergy clearly and with understanding.

Brief summaries of the different sections are again introduced with profit as are the comparative tabulations of differential diagnostic criteria in those conditions showing confusing similarities.

The section in which data are given on the place of occurrence of allergens and the technical procedures peculiar to allergy, is most valuable.

The newly included material on molds and antihistaminics is excellent and is presented with brevity and clarity as is usual with this author. However, the omission of the excellent bibliography included in the original edition represents a distinct loss, and it is unfortunate that the publishers deemed this necessary.

This book will be of great service to all physicians desiring to increase their knowledge of allergy. This should include all members of the profession.

H. M. B.

hardly correct to classify an agnosia among the cranial nerve lesions, even though it is qualified by the reference to the angular gyrus. Actually "optic agnosia" and "word blindness" are not synonymous. On page 7 one finds the statement, "circumferential blindness ('tubular vision') due to hysteria or retrobulbar neuritis." Retrobulbar neuritis notoriously causes a central scotoma and not a constriction of the peripheral fields. Under cranial nerve VIII the authors include, "sensory aphasia—(word deafness)," and "auditory hallucinations" as "symptoms of VIII nerve involvement." Similarly, "motor aphasia" is incorrectly listed among the "symptoms and signs of vagal involvement," as are "psychogenic disturbances." The latter are also included under the cranial nerves XI and XII. Psychogenic disturbances, aphasia, and agnosia involve disturbances of the cerebral cortex, and not of the cranial nerves.

Since this text has been planned to be concise, why the authors pay so much attention to the antiquated terminology commemorating the many pioneers in neurology is hard to understand. Many of the names listed are rarely used. Would it not be best to discourage their employment by omitting them, and using more meaningful designations, even if longer? For instance, under progressive muscular atrophies, among the bulbar types a "Fazio-Londe" syndrome is referred to. Wilson in his encyclopediac text merely refers to these two authors among many others who have described cases of subacute bulbar palsies. Also, why is it necessary to refer to the resistance to stretching the brachial plexus in neuritis of the latter, as Bikel's sign?

While the definitions of many terms are well done, the thumb-nail descriptions of the various disease entities and tumors are hardly sufficient for the beginner, and surely unnecessary for the initiate.

Perhaps the reader harbors a peculiar bias against compendia that make available skeletal material that can be exploited by those who are disinclined to make a more thorough study of neurology, no doubt "Correlative Neuroanatomy," barring its errors, has served many a medical student well in helping him prepare for examination.

H. A. T.

*Obstetric Analgesia and Anesthesia.* By FRANKLIN F. SNYDER. 401 pages; 16 × 24 cm. W. B. Saunders Company, Philadelphia. 1949. Price, \$6.50.

From the author's rich background of clinical and experimental investigation comes this interesting compilation of data concerning the various agents used in obstetrics to produce analgesia and anesthesia. The analysis of the physiologic and pharmacologic factors together with the survey of clinical case reports and conclusions, seemed to the reviewer to be particularly unbiased.

The work is divided into two sections, the first of which, comprising about half of the book, is a rather technical but clear exposition of fetal respiratory physiology and pathology, which proposes to prove that the fetal respiratory system is the site of greatest vulnerability to injury that proves fatal during labor or following it. It is also shown that intrauterine respiratory activity, like that seen after birth, takes place. Thus, breathing begins far back in embryonic life. It is indicated that since the functional significance of fetal respiration has been established, a new approach is open to the analysis of the hazards of labor to the child. The author describes much of his own fundamental experimental work on fetal respiratory physiology including assay of the pharmacologic factor in labor as illustrated by the action of various drugs in obstetric analgesia. He uses fetal respiratory movements as a sensitive indicator which can detect the earliest effect of narcosis. Results are expressed in terms of depression in activity of the fetal respiratory system and by impairment in the effective uterine expulsive mechanism. The first section is a background for the more clinical second section.

- Einführung in die Innere Medizin.* By DR. HANS JULIUS WOLF. 608 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$7.25.
- Das Ekg-ABC: Eine Systematik zur Auswertung von Elektrokardiogrammen.* By MAX WALDHECKER. 114 pages; 21 × 14.5 cm. (paper-bound). 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$2.25.
- Die Erkrankungen des Darmes. Anhang: Die Prokto-sigmoidoskopie.* By WALTER ZWEIG (London). 253 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$6.75.
- Grundlagen zur Erforschung des Alterns.* By DR. PAUL MATZDORFF. 248 pages; 23.5 × 15.5 cm. 1948. Verlag von Dr. Dietrich Steinkopff, Frankfurt/Main, Germany. Price, DM 13,50.
- Die Insulin-lipodystrophie.* By PROF. DR. FERDINAND ADALBERT KEHRER. 50 pages; 21 × 14.5 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$1.50.
- Die Konstitutionellen Vergrosserungen Umschriebener Körperabschnitte.* By PROF. DR. FERDINAND ADALBERT KEHRER. 293 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$8.50.
- Lehrbuch der Haut- und Geschlechtskrankheiten.* By DR. WALTHER SCHÖNFELD. 467 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$7.25.
- Lehrbuch der Klinischen Hämatologie.* By PROFESSOR DR. HANS SCHULTEN. 499 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$11.00.
- Leitfaden der Blutmorphologie.* By LYDIA SCHUDEL. 47 pages; 24.5 × 17 cm. (paper-bound). 1947. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$3.00.
- Die Lungentuberkulose.* By PROF. DR. MED. H. GISSEL and DR. MED. HABIL. P. G. SCHMIDT. 264 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$8.00.
- Marihuana in Latin America: The Threat It Constitutes.* By PABLO OSVALDO WOLFF, M.D., Ph.D., M.A., Buenos Aires, Argentina, Member of Expert Committee on Habit Forming Drugs of the World Health Organization. 56 pages; 20.5 × 13.5 cm. (paper-bound). 1949. Sponsored by Washington Institute of Medicine; published by The Linacre Press, Inc., Washington, D. C. Price, \$1.50.
- Medizinische Klinik ein Fortbildungskurs für Ärzte.* By PROF. DR. FERDINAND HOFF. 467 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$9.00.
- Modern Practice in Psychological Medicine—1949.* Edited by J. R. REES, M.D. 488 pages; 25 × 17 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$10.00.
- Neuere Tuberkuloseforschung I.* By OBERMEDIZINALRAT DR. GRIESBACH, Augsburg. 112 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$2.00.
- Outlines of Internal Medicine.* 6th Ed., First Printing. Edited by C. J. WATSON, M.D., Head, Department of Medicine, University of Minnesota. First four

# COLLEGE NEWS NOTES

## A.C.P. POSTGRADUATE COURSES

A schedule of the courses is repeated on the inside back cover page of this journal.

Although Course No. 1, **CARDIOLOGY**, at the National Institute of Cardiology of Mexico, had a registration of only twenty-five, due to the lateness of the announcement of the course, it was received with enthusiasm. Quoting from some of the reports received from those in attendance: "I spent a very profitable two weeks. The course was well-organized and well-conducted. I was very favorably impressed with the well-trained group of men there. The course gave me just what I wanted."—M.D., Tennessee. "In my opinion, it was the best course in Cardiology which it has been my privilege to attend. Its strong points were (1) the care with which the program was arranged; (2) the coördination between the Director and the heads of each department; and (3) the high level of instruction which each speaker maintained."—M.D., California. "A most profitable course and enjoyable vacation. The course is highly recommended, especially for catheterization technics and angiocardiology."—M.D., Texas. "The course was excellent beyond description. The courtesy of the staff and the zeal and interest of each participant has set a goal difficult to equal."—M.D., New York. "The program arranged by Dr. Chavez was informative and illuminating. Not only will the scientific program be forever remembered but likewise the hospitality of the Director. May I add that the enthusiasm and good fellowship displayed by Dr. George Morris Piersol, Dr. William Dock and Dr. George C. Griffith, American College of Physicians' guests, were deeply appreciated. I wish to express due thanks to The American College of Physicians for granting such opportunities to its members."—M.D., Pennsylvania.

When the course in Cardiology in Mexico is repeated, it is hoped that adequate notice of perhaps six or more months will be given to all members of the College, so that they can take advantage of this outstanding course.

Courses No. 2 and No. 3, **GASTRO-ENTEROLOGY** at the University of Chicago, and **CLINICAL NEUROLOGY** at Jefferson Medical College of Philadelphia; respectively, will have been concluded before the publication of this news item. In each case the registrations were reasonably large and representative. Reports from the men registered are not yet available, but from former experience it can be stated, with assurance, that no better courses in the respective fields could be arranged anywhere. Both courses have been given previously with signal success.

Those wishing to register for the remaining courses on the schedule should do so without further delay. Course No. 6, **THE BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO INTERNAL MEDICINE**, at the University of Wisconsin Medical School, is already registered to capacity and some of the other courses are approaching that point. Especially do Courses No. 7 and No. 8, **BLOOD DYSCRASIAS**, at the Medical College of Alabama, and **THE PHYSIOLOGICAL APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES**, at the University of Southern California School of Medicine, respectively, warrant increased registration, because there are still ample facilities available. Detailed outlines of all courses can be obtained from Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

---

## RESEARCH FELLOWSHIPS OF THE AMERICAN COLLEGE OF PHYSICIANS

Some months ago The American College of Physicians announced a limited number of Fellowships in Medicine and/or Pediatrics available from July 1, 1950

held at the Hotel New Yorker, New York City, November 14-18, 1949. The announcement states that the course is given with the coöperation of members of the staffs of the New York City medical schools and hospitals. Fee for the course is \$50.00. Information can be obtained from the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Ill.

---

#### POSTGRADUATE COURSE IN CARDIOLOGY AT DALLAS

A postgraduate course in Cardiology presented under the coöperation of the Dallas Academy of Internal Medicine, the Dallas Heart Association and the Faculty of Southwestern Medical School will be conducted at Dallas, November 28-December 1, 1949. The course will be held at the Melrose Hotel and Parkland Hospital. Applications for registration should be sent to the Dallas Southern Clinical Society, 433 Medical Arts Bldg., Dallas 1, Tex.

---

#### COURSE IN CLINICAL CYTOLOGY

McGill University and the Royal Victoria Hospital, Montreal, announce a two-weeks course in individual instruction in Cytological Technics and Interpretation, November 7-21, 1949, under the direction of Dr. J. Ernest Ayre. The tuition fee is \$100.00.

---

#### RESEARCH GRANTS AND FELLOWSHIPS TO BE MADE AVAILABLE IN 1950 BY THE LIFE INSURANCE MEDICAL RESEARCH FUND

Applications for 1950 grants in aid of research on cardiovascular problems will be received by the Life Insurance Medical Research Fund up to January 1, 1950. Support is available for physiological, biochemical, and pathological research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about \$550,000 will be awarded for these grants.

Applications for postgraduate fellowships for training in research in 1950-51 will also be received by this Fund up to January 1, 1950. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.) or the equivalent is required. The annual stipend varies, as a rule being between \$3,000 and \$4,000, with larger amounts in special cases. At least 12 postgraduate fellowships will be available.

New grants and fellowships will become available on July 1, 1950.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29, New York.

A number of pre-doctoral fellowships for basic training in research will also be awarded. Details are available on request.

---

#### FEDERAL GRANTS FOR NATIONWIDE ATTACK ON HEART DISEASE

The United States Public Health Service and the National Heart Institute recently announced grants of federal funds amounting to \$8,614,737 to 85 medical schools and research institutions in 34 states and the District of Columbia. Admin-

Dr. Roscoe L. Pullen, F.A.C.P., Seattle, Wash., has been appointed Professor of Graduate Medicine, Director of the Division of Graduate Medicine, and Vice-Dean of Tulane University of Louisiana School of Medicine, New Orleans, effective October 1, 1949.

---

Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, has succeeded Dr. Hugh J. Morgan, F.A.C.P., Nashville, as a member of the American Board of Internal Medicine.

---

Dr. William Walter Hargrave, (MC), USN, F.A.C.P., retired from active duty in the Navy on October 1, 1949, with the rank of Commodore. His last duty assignment was that as Senior Medical Officer and Head of the Department of Hygiene at the U. S. Naval Academy, Annapolis. Dr. Hargrave is now the Health Officer for the Campbell-Charlotte Health District, Rustburg, Va.

# ANNALS OF INTERNAL MEDICINE

---

VOLUME 31

NOVEMBER, 1949

NUMBER 5

---

## THE ETIOLOGY OF RHEUMATIC FEVER \*

By HOMER F. SWIFT, M.D., *New York, N. Y.*

ALTHOUGH a causative rôle of streptococcal infections with respect to rheumatic fever is fairly widely accepted, the evidence for this opinion seems insufficient for the hypercritical. There are at least three attitudes concerning this question: (1) Acceptance of the thesis and a readiness to apply it practically to public health aspects of the problem; (2) Relative indifference to the information that has been laboriously collected and correlated; (3) Skepticism and reiteration of the statement that the cause of this disease is unknown, or claims that an unidentified virus is the offending agent. It is imprudent to belittle the rôle of a devil's advocate in any philosophical, political, or scientific discussion, for when he performs his task wisely, he will prevent proponents of a thesis from falling into errors, which may have serious and even fatal repercussions in the medical disciplines. It is important, nevertheless, not to allow his arguments to overwhelm the significance of careful observations and thus prevent their effective utilization. In current propaganda and appeals to the public for funds to support research in this disease, it is wise not to have assertions of our ignorance belittle the importance of well established data. Because these data may not appear simple in their relationships, there is danger that they may be ignored and their practical significance be neglected. The purpose of this lecture is to assemble various elements in the puzzle of the rheumatic fever problem and to arrange them in a satisfactory design, with the qualification that the nature of science is to grow and rearrange the elements forming its structure.

Probably the discovery of the action of salicylates in alleviating the toxic and painful manifestations of rheumatic fever materially hindered fundamental investigation of this disease. The symptomatic relief induced created a false sense of accomplishment; and not until several decades after

---

\* Kober Lecture, delivered at Georgetown University Medical Center, Washington, D. C., March 28, 1949.

Delivered in part before the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., April 1, 1949.

From the Hospital of The Rockefeller Institute for Medical Research, New York City.



A forward step in streptococcal classification resulted from Schottmüller's blood agar plate technic for distinguishing hemolytic from nonhemolytic streptococci,<sup>3</sup> and the demonstration that the former comprised the more virulent strains. The frequent association of subacute bacterial endocarditis (endocarditis lenta) with chronic rheumatic valvular disease led many physicians to conclude that both conditions had as common causative agents the nonhemolytic streptococci which induced the finally fatal infection. This opinion was supported by the occasional post mortem recovery of viridans streptococci from the heart's blood of rheumatic subjects, for formerly bacteriologists little appreciated how rapidly, during the death agony or post mortem, green streptococci or enterococci may invade the blood stream from the mouth or intestines where they normally reside. Moreover, the temporary entrance into the blood of lowly virulent nonhemolytic streptococci following nose and throat operations, tooth extractions, instrumentation of the urethra or ureters, or manipulation of intensely inflamed pharyngeal tissues are phenomena, discovered in the past three decades, that explain the occasional recovery of green streptococci from the blood of rheumatic patients during life. It is, indeed, readily understandable how rheumatic fever-inducing properties were attributed to lowly virulent nonhemolytic streptococci, because the lesions they induce are usually nonpurulent, a characteristic of those of rheumatic fever; while in contrast, hemolytic streptococci are often pyogenic. Indeed, the impossibility of demonstrating pyogenic streptococci either in cultures of rheumatic exudates or proliferates, or microscopically in the visceral, articular, or subcutaneous lesions of rheumatic fever patient are features that could blind investigators to their potential pathogenic rôle in this disease. It appeared probable, moreover, that if the rheumatic lesions were invaded by streptococci, such lesions would more readily dispose of the easily phagocytatable viridans varieties than of the more virulent pyogenic hemolytic strains. Indeed we formerly attributed to the viridans streptococci a possible etiologic rôle in rheumatic fever, an opinion that now seems incorrect; but it stimulated animal experimentation and the study of the host-parasite relationships which eventually seem to have added to knowledge concerning this disease. Before discussing these experiments, it is advisable to orient ourselves concerning modern streptococcal bacteriology.

In the early 1920's the classification of streptococci was based mainly upon three general procedures: (1) determining their action on blood; (2) testing their ability to attack certain chemical substances of known composition which were added to artificial culture media; and (3) ascertaining their capacity to survive under critical chemical and thermal environments.<sup>4</sup> While identification on such biochemical bases is sometimes definitive, notably with *Streptococcus mastitidis*, *Streptococcus equi*, the enterococci and *Streptococcus lactis*, many other streptococci have several common biochemical capacities but different pathogenic potentialities; hence the resulting

## SOMATIC ANTIGENIC COMPONENTS

Groups are recognizable serologically because the strains within a group elaborate in common a group specific carbohydrate called C which gives a precipitin reaction in vitro when combined with its group specific antibody. Many groups are further divisible into serological types. The type specific components are sometimes polysaccharides, for example in group B, and sometimes, notably in group A, they are proteins which are designated type specific M substances.

The typing of group A streptococci stems primarily from the ability of a particular strain to induce in animals the ability to resist infection with that strain and also with other strains that elaborate a homologous type specific M protein. This resistance or type specific immunity may be actively induced by nonlethal infections, and also by parenteral injections of vaccines prepared from strains elaborating type specific M protein, but not from strains lacking this capacity. The serum of actively immunized animals

TABLE II

## Somatic Antigens of Group A Streptococci

Somatic Antigens	Antibodies	Specificity
C carbohydrate	Anti C precipitins	Group specific
Nucleoproteins	Antinucleoproteins	Common to many cocci
proteins	Anti T agglutinins	Some type specific; some common to several types
M proteins . . . . .	Type specific	Type specific
	Protective	in vivo
	Bacteriostatic	in vitro
	Anti M precipitins	in vitro*
	Anti M agglutinins	in vitro*

\* With properly absorbed sera.

when injected in sufficient quantities into other animals protects them from infections with streptococci belonging to homologous types, but not from heterologous types.

Sera having this type specific protective capacity contain type specific antibodies. Of these, the most easily recognizable in vitro are anti M precipitins, which form precipitates after mixing suitable extracts of the streptococci in question with properly absorbed sera from highly immunized rabbits. Sera of men or animals infected with group A streptococci, or immunized with these bacteria, also contain agglutinins which may have type specific significance, provided accompanying non-type-specific agglutinins are suitably absorbed from the sera. This important proviso requires attention because many group A streptococci contain another somatic agglutinogen, called T, that sometimes bears a close type relationship to an accompanying M protein, and at other times does not. For example, types 4, 24, 26, 28, 30 and 44 elaborate T antigens so closely related that on the basis of agglutination tests with unabsorbed sera no single one of these types

extracts containing only M protein, for they usually contain residual antigenic substances that yield cross reactions with unabsorbed sera. In fact, suitable extracts prepared from group A hemolytic or viridans streptococci, pneumococci, or even staphylococci contain nucleoproteins which give cross complement fixation reactions with the sera of animals immunized with several varieties of streptococci, and with sera of patients suffering from subacute viridans streptococcal endocarditis, from acute group A streptococcal respiratory infections, or from pneumococcal pneumonia.<sup>9</sup> These results indicate that, in addition to the group or type specific components, the several members of the coccus family form somatic antigenic mosaics containing nucleoprotein-like substances with similar chemical configuration. Such phenomena point to the need for caution in interpreting the significance of both in vivo and in vitro tests performed with only partially purified streptococcal extracts.

### EXTRACELLULAR ANTIGENIC COMPONENTS

The serological reactions just discussed involve somatic antigens contained in streptococcal cells. Human subjects and animals while undergoing group A streptococcal infections or artificial immunizations, often form antibodies against extracellular products of streptococci. These extracellular antigens are elaborated into media nurturing these microorganisms and into the tissues of animals harboring them. Among the many extra-

TABLE III  
Extracellular Antigens of Group A Streptococci

Extracellular Antigens	Antibodies	Relative Antibody† Production in Human Infections	
		No RF	RF
Streptolysin O	Antistreptolysin O	++	+++
Streptolysin S	Antistreptolysin S	++	+
Streptokinase (Fibrinolysin)	Antistreptokinase	++	+++
Hyaluronidase (Types 4 and 24) (Hyaluronidase precursor?)* all types	Antihyaluronidase	++±	++++
Proteinase	Antiproteinase	(+)?	(+±)?
Desoxyribonuclease (Dornase)†	Anti-DORNase†	+	++
Ribonuclease	Antiribonuclease	?	?
Erythrogenic toxin	Antitoxin	?	?

\* The existence of a precursor is assumed because of the frequent stimulation of streptococcal antihyaluronidase following most group A streptococcal infections.

† The abbreviation DORN is derived from DesOxyRiboseNuclease (Tillett et al.).

‡ The designation "relative" refers to statistical analysis of groups of patients and not to one individual.

cellular antigens, those longest studied are erythrogenic toxins, streptolysin O, and fibrinolysin, more accurately designated streptokinase; others have more recently attracted attention.

It is now generally accepted that scarlet fever is caused by group A streptococci that elaborate a rash-inducing toxin against which the patient possesses no effective antitoxic immunity when infected. This toxin cir-

tritional environment by group A streptococci and their respective antibodies require consideration.

Hyaluronic acid, hyaluronidase and antihyaluronidase have recently attracted considerable attention with respect to a possible pathogenic relationship in rheumatic fever. This acid, a highly viscid polysaccharide, makes up the capsules formed by many streptococci belonging to groups A and C.<sup>15</sup> Its presence bears close relationship to the virulence of "animal" group C streptococci,<sup>16</sup> but it has only slight significance in the virulence of group A strains.<sup>17, 18</sup> Hyaluronic acid is widespread in the bodies of vertebrates, notably in the umbilical cord, vitreous humor, synovial fluid, and in the interfibrillar cement substance of collagen.<sup>15</sup> Enzymes that split it are designated hyaluronidases, and several have been described from different sources: leech heads, mammalian testicular extracts, groups A and C streptococci, pneumococci, staphylococci and clostridia. While the common action of the enzymes from these different sources is to split any hyaluronic acid into less complex and viscid products, each hyaluronidase appears to be antigenically specific according to its respective origin; e.g., antihyaluronidase in the serum of persons infected with group A streptococci does not react with hyaluronidase from other bacteria. Three technics for demonstrating hyaluronidase have been employed: mucin clot solution; turbidity reduction; and as a spreading factor (Duran-Reynals<sup>19</sup>). Antibodies against hyaluronidases are measured by their ability to prevent these actions. With the mucin clot prevention technic and a substrate from umbilical cords, hyaluronidase production has been demonstrable only with type 4 and type 22 group A streptococci<sup>20</sup>; but Pike,<sup>21, 22</sup> employing the turbidity reduction technic with hyaluronic acid from streptococcal capsules, found hyaluronidase production by over half of his noncapsulated group A strains and even by some capsulated strains. The possibility that most group A strains form this enzyme, usually as a precursor must be entertained, for although it is difficult of demonstration *in vitro*, the fact that most patients infected with group A streptococci elaborate streptococcal antihyaluronidase indicates its widespread occurrence in these microorganisms. The degree of this antibody response, moreover, suggests that hyaluronidase is a very strong antigen, possibly the strongest of the extracellular antigens.

New born babies have practically the same streptococcal antihyaluronidase content in their sera as is present in that of their mothers; but this disappears within six months. Beginning in the three to five year age period, this antibody begins to appear with a slowly increasing frequency, until the age group of 20 years. The relative frequency curve then remains constant until the 60 year age group, when it falls slightly.<sup>23, 24</sup> This phenomenon, and the demonstration of antibodies against erythrogenic toxin slowly increasing with age, reflect roughly the occurrence of group A streptococcal infections in a considerable portion of the population.

Carefully gathered data moreover have demonstrated that the precursory streptococcal infection may be so mild as to escape clinical detection. For example, Kuttner and Krumwiede<sup>35</sup> showed that during epidemics in a closed institution, streptococci appeared for a few days in the nasopharynges of some children, who then sometimes had slight leukocytosis, and subsequently developed in their sera increasing titers of antistreptolysin O. Others have confirmed this observation under epidemic conditions. Thus was explained the old observation that rheumatic fever occurs at times without an obvious nasopharyngitis as a forerunner: it may be too mild for accurate clinical detection.

#### REACTIONS IN PATIENTS' SERA WITH EXTRACELLULAR STREPTOCOCCAL ANTIGENS

The streptococci inducing the precursory infection, moreover, disappear from the nose and throat before the onset of the rheumatism in a quarter to a third of the patients; hence other evidence of the precursory streptococcal activity is requisite; and the need has been supplied mostly by study of antibodies against the extracellular antigens of group A streptococci. Among these the antistreptolysin O test, devised by Todd,<sup>10</sup> has been most extensively employed; and with it between 80 and 90 per cent of rheumatic fever patients have been shown to develop abnormal amounts of antistreptolysin O in their sera. This is also true of most patients infected with group A streptococci; hence, this reaction is not diagnostic of rheumatic fever, but of group A streptococcal infections. That such infections may occur without inducing antistreptolysin O formation has already been noted; hence this test has only relative, not absolute value.

The application of technic for detecting antifibrinolysin,<sup>12</sup> and more recently for titering antistreptokinase quantitatively,<sup>14</sup> has still further confirmed the nature of the precursory respiratory infection, for sometimes there is an increase in antistreptokinase but no rise in antistreptolysin O, and vice versa. Several observers have reported a relatively higher content of these two antibodies in rheumatic than in non-rheumatic subjects, without having information concerning the antigenic composition of the streptococci infecting their patients; hence it was not known definitely whether the relatively greater antibody formation by the rheumatic group was due to differences in the parasites' activities or in the hosts' responses.

This question is apparently answered by the observations of Anderson, Kunkel, and McCarty<sup>36</sup> in a study of an epidemic in patients infected with strains of one or more of three different types of group A streptococci; so the antigenic stimulus was probably similar. Although, as in all such studies, there was marked variation among individuals, the group which had rheumatic sequelae developed distinctly more antistreptolysin O and antistreptokinase than did those who remained free of rheumatism. Other noteworthy observations were recorded: (1) those patients effectively treated

trary to experience: although it has been demonstrated that among group A streptococci only types 4 and 22 produce hyaluronidase in amounts sufficient to be easily detected in vitro, nevertheless, in at least two epidemics caused by type 4 streptococci in rheumatic subjects, no rheumatic recurrences were induced, while rheumatic fever frequently follows infections with streptococci that produce relatively little hyaluronidase. Furthermore, group C streptococci, quite frequent producers of considerable amounts of hyaluronidase, have likewise not been observed to induce rheumatic fever; and pneumococci, staphylococci and clostridia, also potent producers of this enzyme, are conspicuously negative as inducers of rheumatic fever.

The report by Guerra<sup>40</sup> that hyaluronidase (probably in testicular extracts) acted as a spreading agent (Duran-Reynals<sup>19</sup>) more powerfully in rheumatic fever subjects than in non-rheumatics, and that this spreading action is inhibited in guinea pigs by salicylates, has also excited renewed interest in the possible hyaluronidase-antihyaluronidase question with respect to rheumatic fever. Harris and Friedman<sup>41</sup> employing relatively weaker concentrations of streptococcal hyaluronidase were unable to demonstrate any unusual susceptibility to this spreading factor in rheumatic fever subjects compared with non-rheumatics. They suggest that the differences in their results from Guerra's were due to the strong irritating effects of the extracts used by the latter, and that these nonspecific effects might easily lead to misinterpretation of the results he observed.

Until more light is thrown on the whole hyaluronidase subject, it seems well to assume that the relatively more marked antihyaluronidase formation by rheumatic fever patients, compared with that of patients with simple streptococcal infections, is a concomitant rather than a causal phenomenon with respect to rheumatic fever.

The question of antistreptolysin S production by rheumatic fever patients has received relatively little attention, probably because of technical difficulties in producing this antigen for in vitro studies. Todd, Coburn and Hill<sup>42</sup> reported that antistreptolysin S was more abundant in the sera of patients suffering from simple group A streptococcal infections than in that of patients with rheumatic sequelae, even though the latter contained more than was found in normal persons' sera. With better methods for preparing streptolysin S, reported by Bernheimer,<sup>29</sup> investigations of the relationship of this lysin to various manifestations of streptococcal infections will probably be resumed.

The occurrence in a patient's serum of antibodies against the extracellular components of group A streptococci merely indicates a previous infection with some strain belonging to this group, but has no significance with respect to any particular strain or type. Furthermore, the finding of abnormal concentrations in a single serum is not definitely indicative of a recent streptococcal infection, because fairly high titers of antistreptolysin O, anti-streptokinase, or streptococcal antihyaluronidase may persist in a patient's serum for many months, possibly years, after a streptococcal infection. If

tions, and the quantitative antistreptokinase test was not yet available; but a study of the comparative development of the other three antibodies was possible. The rheumatic fever group developed relatively average higher antibodies than did the non-rheumatic group when tested with these four different technics. Although the average measurable antibodies against the extracellular antigens appeared at practically the same time following infection in all groups of patients, there was an average delay of approximately two to three weeks in the appearance of antibodies against the somatic antigens among the rheumatic fever group as compared with the non-rheumatic; this is illustrated in the bacteriostatic and anti M precipitin tests, and confirms earlier less extensive studies.<sup>44, 45</sup> The possible significance of this delay in the pathogenesis of rheumatic fever is not as yet evident.

Chart 2, summarizing graphically the antibody production by a comparable series of our patients indicates that the more tests that are applied to the same lot of sera, the more convincing is the evidence of a previous recent

Distribution of 4 different antibodies  
in 83 patients infected with Group A streptococci

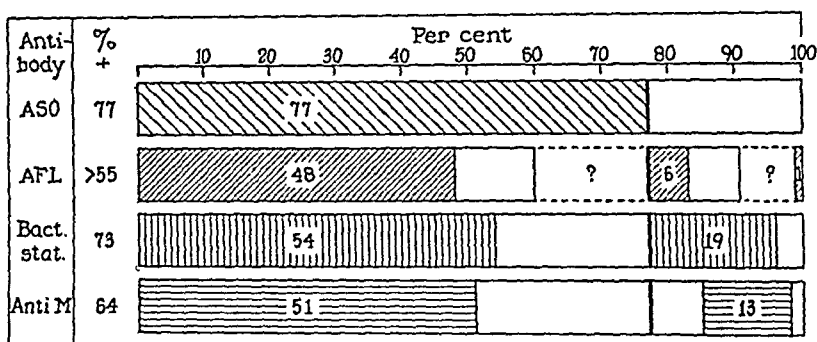


CHART 2.

streptococcal infection. Among patients undergoing 83 different group A infections, whose sera were repeatedly tested for antistreptolysin O, antifibrinolysin, bacteriostatic and anti M precipitin reactions, it was found that the first appeared in practically three-fourths of the cases; but among the patients' sera containing no antistreptolysin O, there was nevertheless a demonstrable formation of antifibrinolysin, bacteriostatic antibodies, or anti M precipitins; hence application of four tests indicates there was antibody formation against one or more streptococcal antigenic components in all instances.

A detailed analysis of this entire series of patients in whom it was possible to initiate the investigations very near the time of onset of their streptococcal infections and to continue them through the period when rheumatic sequelae were apt to occur, and in the event of the appearance of these sequelae for several months and sometimes for two or three years, showed the following: at the onset of an infection with a given type of group A streptococci, a patient's serum contained no bacteriostatic antibodies against that type, al-

demonstration that in one person suffering from repeated respiratory streptococcal infections, each attack has been induced by a group A streptococcus different in type from those shown to have caused previous attacks. This leads directly to the concept that in many people suffering from successive streptococcal infections, each infection is probably induced by group A streptococci different in type from those that caused prior infections in that person.

The varieties of nosologically definable diseases induced in human beings by group A streptococci are probably more numerous than is the case with any other microorganism. None of them, e.g., erysipelas or scarlet fever, is caused exclusively by a single serological type of streptococcus. The characteristic rash of scarlet fever is a peculiar response to an erythrogenic toxin elaborated by strains belonging to several types. Surgical or obstetrical streptococcal infections owe their peculiarity in part to the body areas invaded by the microorganisms, and in part to their virulence. In a streptococcal epidemic due to a single strain, such as occurs in milk-borne infections, and in families, institutions and barracks, many different clinical manifestations are observed; and this suggests that variations in the tissues of different persons are factors which help to condition the clinical pictures.

Powers and Boisvert<sup>49</sup> have outlined the changing types of response to streptococcal infections of the respiratory tract encountered at various age periods. In the very young, the symptoms are least clear cut; the nasopharyngitis is diffuse, of several weeks' duration, and prone to spread to the accessory sinuses and middle ears. The picture may be so noncharacteristic that its etiology can only be determined bacteriologically. Not uncommon is eczematoid dermatitis or vaginitis due to the same streptococci that are inducing upper respiratory infection. In school children, the nasopharyngeal response is somewhat more circumscribed and intense, the general symptomatology more stormy, the duration of a single infection shorter than in the very young. At the end of the first and in the second decade, especially after puberty, the course is usually still more acute, the fever higher, the duration shorter, the nasopharyngeal response more focalized and intense. Such turbulent and relatively brief acute courses exemplified by an attack of tonsillitis, are common in the third and fourth decades of life; and after 40, streptococcal respiratory infections are relatively much rarer than in the earlier age periods, which suggests that with advancing age a fairly effective immunity has developed.

Because these trends of streptococcal diseases towards localization resemble comparable phenomena seen in tuberculosis, Powers has designated the whole group of streptococcal diseases, "streptococcosis." It seems to me that because of the multiplicity of their clinical manifestations they may be more usefully compared with those of syphilis. This disease is currently so modified by antibiotics and other drugs that its normal evolution is difficult to observe.

In untreated or poorly treated syphilitic patients, the first response at the site of inoculation is a hard chancre, which is followed within a few weeks by



this has been one of the objectives of experiments in our laboratories; and while there were many failures in attaining the primary objective, still much information was obtained which, with simultaneous studies of streptococcal infections in rheumatic patients, has apparently advanced our conception as to how streptococci may act to induce this disease. The pertinent data deriving from those investigations follow.

The earlier researches were carried out with rabbits infected intracutaneously with viridans streptococci. By employing suitable strains, it was shown that after the primary inflammatory response had subsided there often appeared, at the sites of the original inoculations, secondary reactions lasting for one to five days.<sup>50</sup> These reactions resembled somewhat those described by Koch in guinea pigs infected with tubercle bacilli, and in many respects differed from the Arthus phenomenon in rabbits injected with foreign serum.<sup>51</sup> This state of bacterial hyperreactivity could be distinctly increased and prolonged by repeated minute focal inocula of the streptococci. Indeed, it seemed to derive, to a considerable degree, from inflammatory foci, for when comparable doses of the same lowly virulent streptococci were injected intravenously into rabbits the focal responses to subsequent intracutaneous inoculation were less marked than in normal controls; in other words a state of immune hyporeactivity had been induced. It was next shown that by injecting lowly virulent strains of hemolytic streptococci, or heat-killed cultures, the state of hyperreactivity was induced by intracutaneous inoculation and a state of immune hyporeactivity by intravenous injections.<sup>52</sup> It was then found that although rabbits immunized intravenously with a strain of viridans streptococci developed a state of immune hyporeactivity to intracutaneous challenge with that strain, their response to a simultaneous challenge with a group A or a group C strain was that of hyperreactivity.<sup>53, 54</sup> Also noteworthy was the observation that two or three months after stopping the intravenous immunization, there developed a state of hyperreactivity to challenge with the immunizing strain.<sup>54</sup> Subsequently, when the significance of successive human infections with several different serological types of group A streptococci was appreciated, it was shown that prolonged intravenous immunization of rabbits with one type of group A streptococci or repeated intracutaneous infections with one fairly virulent type, usually induced the animals' tissues to respond subsequently to suitably sized intracutaneous inocula as follows: immune hyporeactivity to challenge with homologous type strains; and frequently, though not always, the same animals showed cutaneous hyperreactivity to inoculation with heterologous type strains.<sup>55</sup>

#### RHEUMATIC FEVER-LIKE CARDITIS FOLLOWING SUCCESSIVE INFECTIONS WITH DIFFERENT TYPES OF GROUP A STREPTOCOCCI

The probable import of one person having several streptococcal upper respiratory tract infections each with a different type of group A streptococci was at that time becoming increasingly insistent, for it seemed that with each

the adrenal cortex and the occurrence of myocardial granulomata in the rabbits dying, or sacrificed while sick, following the last of several cutaneous streptococcal infections. Several different sets of controls indicate that the experimental conditions apparently conducive to the induction of the lesions described were successive focal lesions caused by group A streptococci of different serological types.

From the results of these experiments it would seem unwise to assume, unreservedly, that rheumatic fever had been induced in these rabbits; but, on the other hand, to deny this possibility, in view of the data presented, would also be unjustified. Those investigators, notably Klinge and his collaborators<sup>57</sup> and Rich and his coworkers,<sup>58</sup> who have emphasized many points of similarity between the carditis seen in rabbits receiving one or more injections of foreign protein and that of rheumatic fever, have argued that these histopathological analogies indicate an "allergic factor" as being common to the two pathological states. It has been emphasized by Ehrlich et al.,<sup>59</sup> however, that there are enough histological diversities in the two conditions to indicate that they are not strictly comparable. Many years ago, in discussing Klinge's investigations, Aschoff<sup>60</sup> emphasized the hazard of attempting to establish the causation or essential nature of a disease by comparing one or two points of analogy with those of another disease. He insisted, that to prove a common causative factor in two such comparable conditions, a single common stimulus must be employed.

In investigating a possible etiological rôle of suspected microorganisms in a given disease and in planning a working hypothesis to test whether, and how, these microorganisms may induce this disease experimentally, it would seem quite important to duplicate, as closely as possible, the particular chain of circumstances under which these agents appear to induce the typical disease in nature. In the earlier part of this lecture are outlined the data obtained from applying current knowledge of group A streptococci and their antigenic components to the bacteriological and immunological studies of rheumatic fever patients; in the latter part is summarized how these data have been utilized in studying experimental streptococcal infections in rabbits. Eventually, by imposing on these animals infectious conditions approximately similar to those observed among rheumatic fever patients, there has been induced a histopathological picture in their hearts closely resembling that of human rheumatic carditis. The small proportion of infected rabbits showing this picture roughly approximated the relative frequency of rheumatic fever encountered among patients infected with group A streptococci.

On the basis of these investigations and of the hypothesis employed in planning them, there seems to be furnished additional support to the theory that group A streptococci are important factors in the pathogenesis of rheumatic fever; and the investigations also indicate how these microorganisms may act in giving rise to this disease.

25. ELLIOTT, S. D.: A proteolytic enzyme produced by group A streptococci with special reference to its effect on the type-specific M antigen, *Jr. Exper. Med.*, 1945, lxxxi, 573.
26. McCARTY, M.: The occurrence of nucleases in culture filtrates of group A hemolytic streptococci, *Jr. Exper. Med.*, 1948, lxxxviii, 181.  
Personal communication about antibody formation by patients.
27. WATSON, R. F.: Personal communication.
28. HERBERT, D., and TODD, E. W.: The oxygen-stable haemolysin of group A haemolytic streptococci (streptolysin S), *Brit. Jr. Exper. Path.*, 1944, xxv, 242.
29. BERNHEIMER, A. W., and RODBART, M.: The effect of nucleic acids and of carbohydrates on the formation of streptolysin, *Jr. Exper. Med.*, 1948, lxxxviii, 149.
30. COBURN, A. H.: The factor of infection in the rheumatic state, 1931, Williams and Wilkins Co., Baltimore.
31. SHELDON, W.: On acute rheumatism following tonsillitis, *Lancet*, 1931, i, 1337.
32. SCHLESINGER, B.: The relationship of throat infection to acute rheumatism in childhood, *Arch. Dis. Child.*, 1930, v, 411.
33. GRIFFITH, F.: Types of haemolytic streptococci in relation to scarlet fever, *Jr. Hyg.*, 1926, xxv, 385.
34. GLOVER, J. A., and GRIFFITH, F.: Acute tonsillitis and some of its sequels; epidemiological and bacteriological observations, *Brit. Med. Jr.*, 1931, ii, 521.
35. KUTTNER, A. G., and KRUMWIEDE, E.: Observations on the effect of streptococcal upper respiratory infections on rheumatic children—a three-year-old study, *Jr. Clin. Invest.*, 1941, xx, 273.
36. ANDERSON, H. C., KUNKEL, H. G., and McCARTY, M.: Quantitative antistreptokinase studies in patients infected with group A hemolytic streptococci: a comparison with serum antistreptolysin and gamma globulin levels with special reference to the occurrence of rheumatic fever, *Jr. Clin. Invest.*, 1948, xxvii, 425.
37. FRIOU, G. J., and WENNER, H. A.: On the occurrence in human serum of an inhibitory substance to hyaluronidase produced by a strain of hemolytic streptococcus, *Jr. Infect. Dis.*, 1947, lxxx, 185.
38. QUINN, R. W.: Antihyaluronidase studies of sera from patients with rheumatic fever, streptococcal infections, and miscellaneous non-streptococcal diseases, *Jr. Clin. Invest.*, 1948, xxvii, 471.
39. HARRIS, T. N., HARRIS, S., and NAGLE, R. L.: Studies in the relation of the hemolytic streptococcus to rheumatic fever. VI. Comparison of streptococcal antihyaluronidase with antibodies to other streptococcal antigens in the serum of patients with rheumatic fever and acute streptococcal infection: mucin clot prevention test, *Pediatrics*, 1949, iii, 482.
40. GUERRA, F.: Hyaluronidase inhibition by sodium salicylate in rheumatic fever, *Science*, 1946, ciii, 686.
41. HARRIS, T. N., and FRIEDMAN, S.: Studies in the relation of hemolytic streptococci to rheumatic fever. IV. Effect of streptococcal spreading factor in rheumatic patients and others, *Am. Jr. Dis. Child.*, 1949, lxxvii, 561.
42. TODD, E. W., COBURN, A. F., and HILL, A. B.: Antistreptolysin S titres in rheumatic fever, *Lancet*, 1939, ii, 1213.
43. ROTHBARD, S., WATSON, R. F., SWIFT, H. F., and WILSON, A. T.: Bacteriologic and immunologic studies on patients with hemolytic streptococcal infections as related to rheumatic fever, *Arch. Int. Med.*, 1948, lxxxii, 229.
44. SWIFT, H. F., and HODGE, B. E.: Type-specific anti-M precipitins in rheumatic and non-rheumatic patients with hemolytic streptococcal infections, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 849.
45. COBURN, A. F.: Observations on the mechanism of rheumatic fever, *Lancet*, 1936, ii, 1025.
46. WATSON, R. F., ROTHBARD, S., and SWIFT, H. F.: Type-specific protection and immunity following intranasal inoculation of monkeys with group A hemolytic streptococci, *Jr. Exper. Med.*, 1946, lxxxiv, 127.

# SODIUM SUCCINATE—AN ANALEPTIC FOR BARBITURATE POISONING IN MAN\*

By RICHARD H. BARRETT, M.D., M.Sc., *Hanover, New Hampshire*

THE barbiturates, next to carbon monoxide, are the most frequent source of poisoning, both suicidal and accidental.<sup>2</sup> This may well be attributable to the widespread use of the barbiturate drugs<sup>1</sup> as evidenced by the fact that in 1945, alone, over 290 tons of this one group of hypnotics were produced.

This paper reports an investigation of the effects of a new analeptic agent, sodium succinate, in the treatment of poisoning with barbituric acid compounds.

The present and generally accepted treatment of barbiturate poisoning<sup>3</sup> consists of one or all of the following procedures with, possibly, others: (a) Administration of oxygen, alone or in combination with carbon dioxide, to combat anoxia; (b) administration of intravenous fluids, to increase, supposedly, kidney filtration and thereby remove the barbiturate, at an increased rate; (c) gastric lavage, employed very early, in an attempt to remove the depressant drug, provided it were ingested; and (d) probably the most outstanding of all, the use of various convulsant drugs given intravenously. Picrotoxin, an outstanding example of the convulsants, first came into general usage in 1936. Since that time, it has been the drug most commonly used in the treatment of barbiturate poisoning.<sup>4</sup>

One may accept readily the use of oxygen and certain intravenous fluids as supportive therapy. However, gastric lavage should be used rarely, if ever, on a comatose patient with suspected barbiturate poisoning, because of the danger of inducing vomiting and consequent aspiration of stomach contents.

The use of convulsant drugs in the treatment of barbiturate poisoning while justified in critical situations is not without danger. In accidental and, especially, in suicidal barbiturate poisoning, exact dosage and type of barbiturate consumed is rarely known; therefore, a safe dosage of convulsant is difficult to determine. It has been stated that should a convulsion develop during the use of a convulsant drug, the convulsion may be controlled easily by giving more barbiturate.<sup>4</sup> This procedure could lead to disastrous results. Certain convulsants, given in subconvulsant doses, may prolong the later stages of recovery from the effects of hypnotics, and this secondary depression may be accompanied by pulmonary edema.<sup>5</sup> Hence there is possibility of underdosage, as well as overdosage.

\* Presented at New England Sectional Meeting of the American College of Physicians, January 28, 1947.

From the Hitchcock Clinic, Mary Hitchcock Memorial Hospital, Hanover, New Hampshire.

sibility of a reflex mechanism, based on the hypertonicity of the agent used, has been considered. A brief discussion relative to the possible mode of action of succinate has been presented elsewhere.<sup>3</sup>

Sodium succinate is a hexahydrated salt; therefore, the actual concentration of the solution used was about 18 per cent, rather than 30 per cent. This solution is stable at normal room temperatures (20° to 25° C.) but it becomes less effective or completely ineffective, as an analeptic, if allowed to remain at higher temperatures.

In an earlier report,<sup>3</sup> a series of 70 clinical cases that had received sodium succinate after Pentothal Sodium anesthesia ("controlled barbiturate poisoning") was compared, with a similar series that received only Pentothal. The results of that investigation demonstrated that sodium succinate when used, according to a simple procedure, was definitely effective in shortening the sleeping times of the cases in the experimental series. The results were often quite dramatic.

The purpose of the present investigation was to evaluate the effectiveness of sodium succinate used in man for the treatment of "uncontrolled" (that is, suicidal or accidental) barbiturate poisoning. The effect of the drug in 15 cases was studied. All subjects in this investigation had, or were diagnosed tentatively as having, "barbiturate poisoning"—produced accidentally *or* with suicidal intent. All were from rural areas. They were treated in a community hospital or in the home.

#### METHOD

There was no specific preparation of the barbiturate poisoning cases previous to their initial treatment with sodium succinate. Manual or mechanical removal of any obstruction to the airway was a routine. When indicated, an artificial, pharyngeal or endotracheal, airway was introduced. (The endotracheal tube facilitates proper cleaning of the tracheo-bronchial tree.) The recumbent patient was placed usually in a slightly head-down position. Gastric lavage was *never* used.

Sodium succinate was given intravenously, immediately following the routine, preliminary procedures, just mentioned. The first 3 to 5 c.c. of succinate solution were injected rapidly—usually at the rate of 1 c.c. per second. The remainder of any indicated quantity was given more slowly. There is no fixed dose for sodium succinate; it should be given intermittently as indicated.<sup>3</sup>

Injection was delayed for 10 to 20 seconds after the initial dose. Typically, patients coughed once or twice during that brief pause. The cough was taken as a sign of adequate initial dose. If no cough were produced by the first dose, the dose was repeated. Unanesthetized human volunteers have described the subjective stimulus for the cough as being similar to that sensation which one experiences on taking a large drink of what he expects to be straight gingerale, but which proves to be straight whiskey!

TABLE I  
Sodium Succinate—An Aleptic for Barbiturate Poisoning in Man

Identification	No.	Sex	Age	Type and Dosage of Barbiturate	Narcosis Time			Dosage of Sodium Succinate 3 gm./10 c.c.	Narcosis Time after Succinate Therapy	T.N.T.	Comments
					Outside Hospital	Inside Hospital	Total N.T.				
42438 P. H.	1	M	61	Barbital gr. 125 (8.3 grams)	5°	42°	47°	30 gm. (100 c.c.)	15' opened eyes 45' oriented—to status quo	47°45'	Known psychopath. Negativism and bed boards on awakening.
42903 C. T.	2	F	56	None (cerebrovascular accident)	10°	3°	13°	20 gm. (200 c.c. of 10%)	30'	14°	? of cerebrovascular accident before succinate therapy. Later proved by autopsy.
47840 L. R.	3	F	58	Barbital gr. 150 (10 gm.) Nembutal, 4.5 gr.	28+1°	1°	30°	30 gm. (100 c.c.)	5" cough 2°35' oriented	32-33°	Nembutal taken with one ounce of elixir of phenobarbital. Chin relaxed on admission.
41613 P. C.	4	F	23	Seconal, gr. 19.5 (1.3 gm.)	9-10°	15'	9-10°	42 gm. (140 c.c. 3°)	4° oriented	14°	Pupils exhibit reverse reaction to light, for first 30' of succinate therapy.
30088 A. H.	5	F	66	Nembutal, gr. 13.5 (0.9 gm.) Capritol (?)	2°30'	1°	3°30'	4.5 gm. (15 c.c.)	10" cough 15' turning 20' oriented	4°	(Amyotrophic lat. sclerosis)
42225 R. D.	6	F	64	Phenobarbital (repeated doses) Amt.?	3 days ?	1 day	4 days	4.5 gm. (15 c.c.)	24° oriented	5 days	Pt. had fallen down stairs. Phenobarb. given for relief of physical discomfort (pain). "Memory loss after first or second dose. "Thanks" for reviving.
42226 A. P.	7	F	45	Amytal (amount ?)	10°	7°	17°	6 gm. (20 c.c.)	10" cough 1°30' groan 3' opened eyes	17°3'	Told family she had taken "sleeping pills." They didn't believe her for 10 hours.
50427 A. H.	8	M	66	Pentothal (2.5%) (450 mg. in 15' for surg.	—	7°	7°	3 gm. (10 c.c.)	10" cough 5' tingling in face	7°5'	Normal B. P. 110/70. Before succinate 90/50. After 150/90; then in 5' to 110/70.
46560 M. S. O.	9	F	48	Sod. amytal, gr. 6 (0.4 gm.)	8°	1°	9°	3 gm. (10 c.c.)	20" cough 20' oriented	9°21'	Possible idiosyncrasy to drug or memory loss by pt. re amt. of amytal taken.
48752 P. N.	10	F	40	Phenobarbital, gr. 6.75 daily for 10 years	Semi-com.	Semi-com.	Semi-com.	3 gm. (10 c.c.)	1' (increased depth of respiration)	1°	Pt. exhibiting withdrawal symptoms of chronic barbiturate poisoning.
45863 D. M.	11	F	3	Nembutal, gr. 4½ (0.3 gm.); Phenobarb.; nail polish remover.	2°45"	3°	5°45'	3 gm. (10 c.c.) Initial 15 gm. (50 c.c.) Total in 3°	2' cough 3° oriented	7-8°	Unknown amt. of phenobarb. taken. One ounce of nail polish remover (acetone).
598 A. C.	12	F	38	Nembutal, gr. 15 (1 gm.)	30'	Not in Hosp.	30'	6 gm. (20 c.c.)	15" cough 1' talking	31'	Not admitted to hospital.
47227 L. Y.	13	M	63	Seconal, gr. 27 (1.8 gm.) Divided doses.	10°	20'	10°20'	6 gm. (20 c.c.) Initial 21 gm. (70 c.c.) Total	10" cough 2' oriented	12°30'	Pharmacist. Seconal taken for relief of pain (self treatment). Could be roused but was disoriented. Memory loss.
30487	14	M	61	Pentothal (2.5%) 55 c.c. (1375 mg.) given in 15" for surgery.	—	20'	20'	2.8 gm. (9 c.c.) Initial 6 gm. (20 c.c.) Total	5' groaning 30' moving head and body	50'	Pt. in laryngospasm when succinate given. This stopped in 20".
36718	15	M	60	Pentothal (2.5%) (550 mg.) For surgery.	—	25'	25'	6 gm. (20 c.c.)	1' cough 5' eyes open	30'	Pupils pin point before succinate, dilated after 3 c.c.

° equals hour. ' equals minute. " equals second.

While the patient was being examined, 5 c.c. of 30 per cent sodium succinate were given rapidly, by vein. After five seconds, the patient coughed and moved her right leg. Systolic blood pressure increased by 10 mm.

Three minutes after the initial injection, an additional 10 c.c. of succinate solution were given rapidly. The immediate effect was a marked increase in depth of respiration without any remarkable change in rate. The blood pressure was then 120/80.

During the first 10 minutes of therapy, the patient received 50 c.c. of succinate solution. (This was equivalent to 15 grams of hydrated sodium succinate or 9 grams of the anhydrous form.) Following this dose, the eyelid reflex was present and she was moving her legs. A crimson flush was present in the blush areas.

An intravenous clysis of 10 per cent succinate and 5 per cent glucose was started at a slow drip-rate. Fifteen minutes later, the patient was slightly cyanotic. A large amount of thick, tenacious mucus was removed from the pharynx; the infusion rate was increased; and, for five minutes, 100 per cent oxygen was given by face mask.

Two hours and 35 minutes after the start of succinate therapy, the patient was well oriented and talking coherently. She stated that she had taken "4½ grains (0.3 gram) of Nembutal, and one ounce of elixir of phenobarbital." This, certainly, was *not an excessive dose*, especially considering the fact that, according to her home physician, she was not abnormally susceptible to the usual effects of these drugs; however, two hours later, she "remembered" also 30 five-grain barbitol tablets (150 grains or 10 grams) that she had taken with the other hypnotics.

This woman received 100 c.c. of 30 per cent sodium succinate (30 grams of the hydrous salt) in two hours and 35 minutes.

A three-year-old girl, who, at the time of admission, was comatose, moderately flaccid, and unresponsive to normally painful stimuli, with acetone-like breath and rapid respirations, had signs of pulmonary edema on the right. The child had no history of diabetes and, obviously, was not undernourished.

Total narcosis time before admission was indefinite, but it was not more than two and three-quarters hours.

The history of this case previous to admission was essentially as follows: The patient's five-month-old brother had been, supposedly, having his mid-morning nap. Their mother had been busy with housework until she went into the baby's room to get something. There, she found the patient "sound asleep on the floor," and the baby "wide awake in his crib." Several different types of tablets and pills were scattered on the floor; also, a new, four-ounce bottle of nail polish remover was open and only three-fourths full. The family physician was called and the patient was brought to the hospital.

Three hours after admission there had been no appreciable change in the patient's general condition. The respiratory rate remained rapid and shallow, and the child continued to be comatose and unresponsive.

At this time, 10 c.c. of sodium succinate (30 per cent) were given, in two minutes. During the initial course of the injection, the patient demonstrated the typical cough, following which she swallowed several times. A "succinate flush" appeared on her face and arms. Respirations became deeper.

Two and one-half hours later, an intravenous clysis of 10 per cent succinate and 5 per cent glucose in water was started.

Within the next half-hour, the succinate flush covered practically her entire body. The patient reacted to painful stimuli and opened her eyes, when requested to do so.

Although ataxic, she was well oriented in the following hour and asked for "a good lunch and a big glass of milk." She got both and consumed both. This was less

In several hundred administrations of sodium succinate to man, under various conditions and for various indications, there have never been visible convulsions nor production of excitement, beyond the *status quo* of the subjects concerned.

It has been stated that "patients with barbiturate poisoning fall into four groups, two of which recover and the remaining two do not. The first is the group of patients who recover without any treatment. All they require is general nursing. The second is the group of patients who die regardless of how intensive and expert the treatment is. They have simply taken so large a dose that no antidote or method of treatment can save them. The third group embraces those patients who recover only because of expert management; without the most effective measures most frequently applied they would succumb. The fourth embraces those patients who die because of the treatment."<sup>2</sup> Sodium succinate can be a factor in eliminating the last group and, probably, the second.

It may be helpful to know the amount of barbiturate a patient has taken, but this information is frequently inaccurate. It is, however, well to remember that adults are almost certain to recover, without specific treatment, from oral doses of the order of 1 or 2 grams of any of the commonly used barbiturates. The fatal dose is sometimes stated as being, in general, 15 to 30 times the therapeutic dose. It has been said that the dose of barbital which is nearly always fatal is about 10 grams, and that of phenobarbital, from 6 to 8 grams.<sup>9</sup> However, there are so many factors that may contribute to the depressing effect of the barbiturates, such as physical and mental fatigue, a very recent hot bath, analgesic drugs, etc., that discussions concerning any fixed, or even nearly fixed, so-called "fatal dose" have little, if any, value. Every case of barbiturate poisoning should be treated as an entity—regardless of drug taken, or supposedly taken. The greatest foe in the treatment of barbiturate poisoning is anoxia. The greatest foe in recovery from barbiturate poisoning may be the type of treatment employed.

A few years ago, before the use of succinate, a 17-year-old girl, who had taken an indefinite amount of phenobarbital, was admitted to our hospital. The quantity of drug concerned was estimated, by the referring physician, to be between 150 and 200 grains (10 to 13 grams). At the hospital, it was estimated that she would sleep for a week. She did.

During that entire week her position was changed every half hour, day and night, side to side, foot of bed elevated, then head of bed elevated. Some of the convulsant drugs were used, but only in relatively small doses. Supportive therapy was the main course of treatment. The maintenance of fluid, electrolyte and protein balances became a complicated problem. During the last four days of the week, a constant vigil was necessary. In order to maintain an adequate airway, it was necessary to bronchoscope the patient two or three times to remove thick, tenacious mucus from the tracheo-bronchial tree. Recovery was finally complete, and there were no apparent mental changes. However, it was a very exhausting ordeal, especially from the nursing standpoint. Without conscientious nursing care, recovery for this case would have been impossible. It is for cases of this type, especially, that succinate is indicated.



## BIBLIOGRAPHY

1. Federal officials puzzled by large United States consumption of sleeping pills, *Jr. Am. Med. Assoc.*, 1946, cxxxiii, 405.
2. Departments of Pharmacology and Medicine, Cornell University Medical College and the New York Hospital, Conferences. Conferences on Therapy; Treatment of Barbiturate Poisoning, *Am. Jr. Med.*, 1946, i, 93-103.
3. BARRETT, R. H.: The analeptic effect of sodium succinate on barbiturate depression in man, *Anesthesia and Analgesia*, 1947, xxvi, 74-81, 105-113.
4. DARCEY, J. F.: The picrotoxin treatment of barbiturate poisoning, *Jr. Nerv. and Ment. Dis.*, 1944, xcix, 367-375.
5. BARLOW, O. W.: The relative efficiency of a series of analeptics as antidotes to sublethal and lethal dosages of pentobarbital, chloral hydrate, and tribromethanol ("Avertin"), *Jr. Pharmacol. and Exper. Therap.*, 1935, lv, 1-22.
6. SOSKIN, S., and TAUBENHAUS, M.: Sodium succinate as an analeptic for barbiturate poisoning and in the control of the duration of barbiturate anesthesia, *Jr. Pharmacol. and Exper. Therap.*, 1943, lxxviii, 49-55.
7. CAMPBELL, C. J., MAES, J. P., and BARRETT, R. H.: Sodium succinate as an analeptic in man, *Fed. Proc.*, 1946, v, 15.
8. FITCH, R. H., and TATUM, A. L.: Duration of action of barbituric acid hypnotics as a basis of classification, *Jr. Pharmacol. and Exper. Therap.*, 1932, xlv, 325-335.
9. RICHARDS, RICHARD KOHN: The therapy of barbiturate poisoning, *In: FANTUS, BERNARD: The therapy of the Cook County Hospital*, *Jr. Am. Med. Assoc.*, 1940, cxv, 527-529.
10. ELLIOTT, K. A. C.: The possible rôle of intermediary metabolites as hydrogen carriers. *In: A symposium on respiratory enzymes*, 1942, The University of Wisconsin Press, Madison, pp. 33-35.

As Bywaters<sup>15</sup> pointed out, the disease is really not new. Similar cases had been encountered at least as early as 1909 by Colmers,<sup>23</sup> though they were not recognized. In 1946 Lucké<sup>61</sup> reported an excellent study of observations made on 538 fatal cases of "lower nephron nephrosis," as he called it.

Increased interest in and knowledge of the lower nephron syndrome and some of the acute anurias has resulted in more frequent use of the artificial kidney<sup>55, 56</sup> and other methods for the removal of toxic elements circulating in the blood of the anuric patient. Numerous papers have been published on the subject within the last few years and many more are sure to follow, especially since the possible clinical value of such procedures has been definitely realized.

### THE CLINICAL PICTURE

Before the more fundamental aspects of the lower nephron syndrome are discussed, it is advisable to review the clinical picture.<sup>16, 17, 61</sup> As stated previously, the *causative* agent varies widely. The patient suffering from a crushing injury which produces lower nephron nephrosis presents a history of having been pinned by heavy beams or pieces of masonry in such a manner that a considerable amount of tissue has been crushed. He has usually remained under the crushing force for several hours. As a rule, he appears to be in good condition soon after release except for wounds and local injuries, such as fractures and contusions. However, in a few hours he begins to show evidences of edema and slight oozing and hemorrhage into the injured tissues and from the wounds. He then passes quickly into the *first phase of shock*, which is considered by many to be due to loss of plasma through damaged capillary walls into the tissue spaces of the injured areas. These areas become extremely swollen, and the skin becomes shiny. Evidences of necrosis with bleb formation may appear. Loss of fluid into the tissue spaces results in hemoconcentration, evidenced by an increase in hemoglobin, hematocrit and erythrocyte count. During this phase of shock the skin tends to be pale, cold and moist, although the blood pressure generally remains essentially normal, apparently because of compensatory vasoconstriction. Occasionally when this vasoconstriction is not maintained, there follows a rapid drop in blood pressure, with the development of the *second phase of shock*. If plasma or fluids are administered at this time, the blood pressure will return to normal. With inadequate therapy shock may become irreversible.

The patient tends to show evidences of *anxiety*. The first or second samples of *urine* passed following the injury are noted to be bloody and to contain pigment suggestive of hemoglobin or altered hemoglobin. The urine also contains albumin, creatine, granular casts and pigment granules, which sometimes resemble intact erythrocytes. It is usually highly acid, with a pH of 4.6 to 6.0. The urine volume remains low and may even approach anuria. Oliguria continues despite fluid intake or any form of therapy. The specific gravity tends to become fixed at 1.010, correction having been made for the protein content.

known that damage to cells results in an escape of potassium into intercellular spaces.

If diuresis continues and if renal function progressively improves, the patient will make an apparently uneventful recovery. However, should diuresis fail to develop, there will ensue a continuous downward course, characterized by increasingly severe uremia with extreme mental disturbances, often terminating in coma. The patient often calls out with alarm, becomes pale, sweats profusely and the alae nasi become dilated. Death usually occurs suddenly, sometimes even within one or two minutes. He may recover from these episodes, only to be seized by another an hour or so later—one of them terminating fatally.

The general clinical pattern varies little with the responsible etiologic factors. The chief difference is in that phase of the patient's course concerned directly with the etiologic factors producing the entity. For example, in lower nephron nephrosis eventuating from a transfusion reaction there will be a history of administration of incompatible blood, followed by a severe chill and fever and then oliguria, hematuria, pigment and erythrocyte casts, and uremia, usually with ensuing death. Renal function decreases until the specific gravity is fixed at 1.010, and azotemia with retention of other toxic materials develops. In a patient who suffers a transfusion reaction, particularly postoperatively or as a result of treatment for an accident, various degrees of shock are liable to occur. *Shock* and *vomiting* are two of the associated manifestations which tend to precipitate or aggravate the oliguric state.<sup>10, 61</sup> It is interesting to note that in those patients who sustain such damage without the development of these two symptoms, the severity of the clinical state is not great.

When the lower nephron syndrome is produced by a reaction to sulfonamides, the patient has usually received the drug in the presence of an impaired cardiovascular system, such as congestive heart failure, or impaired renal function, with inadequate urinary output and often in the presence of acid urine.<sup>14, 107</sup> Hematuria occurs, associated with sulfonamide crystals in the urine and sometimes with pain over the renal regions. These patients, as a rule, do not manifest a shock-like state, although occasionally shock or peripheral circulatory collapse may occur, partially as a result of the reaction to the drug and partially as a result of the disease for which the drug was employed. The clinical course and general manifestations are essentially those described previously for the crush syndrome.

The clinical picture of the lower nephron syndrome also resembles that of the uteroplacental syndrome,<sup>108</sup> as encountered in postpartal sepsis or in criminal abortion with infection of the uterus. There is a difference in the clinical pattern due to the infection, but as far as the renal portion of the picture is concerned, it is essentially identical.

In summary, the clinical picture produced by the various disease states is modified in part by the etiologic factors concerned with the production of that

hours, depending upon the rate of development of oliguria. However, the typical manifestations do not usually appear until the last two or three days of life. Vomiting and mental disturbances, such as irrationality, drowsiness and finally coma, are commonly associated symptoms. Convulsions are rare, as in any type of true uremia.

(4) *Fatality Rate.* The fatality rate is extremely high. Once the cardinal signs of oliguria, excretion of heme pigment, azotemia and hypertension develop, it reaches about 90 per cent. The course of the disease is relatively brief, and in fatal blood transfusion reactions the survival period is usually three to 10 days. In the crush syndrome death usually occurs by the end of the first week; most patients surviving eight to nine days recover. In one series<sup>61</sup> 74 per cent of the patients died within the first 48 hours. About 8 per cent of the patients who died have been reported to survive more than 12 days. It is not known whether death is due entirely to renal damage or in part to the precipitating cause itself, but it is quite likely that there are a number of contributing factors.

### PATHOLOGY

The organic changes, other than those which occur at the primary site of injury by the etiologic agent, such as local tissue damage in the case of the crush syndrome or injury to the gastrointestinal tract in the case of mercurial poisoning, are largely confined to the kidneys.

*Gross Appearance of the Kidneys.* There are no pathognomonic gross manifestations of the lower nephron syndrome. The essential gross and microscopic manifestations are as follows<sup>8, 15-17, 30, 61, 74, 77</sup>: The kidneys are usually swollen and increased in weight, in some instances two or more times the normal weight. There has been no definite correlation between the size of the kidneys and the duration of the disease, although a certain amount of time is required for the swelling to develop. There is some suggestion that the increase in size of the kidneys after trauma or burns tends to be greater than that following nontraumatic conditions, such as transfusion reactions. Typically the kidney is somewhat soft, the capsule strips easily, the outer surface is pale, smooth and glistening, and a clear or slightly bloody fluid oozes from the cut surface. The cortex is widened and tends to bulge perceptibly. It is moist, pale and in sharp contrast to the dusky, somewhat cyanotic-appearing medulla. The striations are often greatly accentuated. A whitish stripe has been described in the inner aspect of the cortex.

*Microscopic Findings.* The histologic descriptions, including those of Bywaters and his group,<sup>15-17</sup> Minami,<sup>74</sup> Lucké<sup>61</sup> and Mallory,<sup>69</sup> have been summarized into four essentially distinct categories by Lucké<sup>61</sup>:

(1) There is degeneration and necrosis which involves somewhat selectively the lower part of the nephrons, that is, the thick portions of the loops of Henle and the distal convoluted tubules.

These degenerative changes may result in bulging or even actual rupture of the necrotic portions into the veins. Diverticuli may be observed. Regeneration in various stages of development begins to make its appearance if survival time exceeds three or four days. There may be casting off of segments of epithelium with the growing of new cells beneath the dead lining. In the early stages the protoplasm tends to be basophilic and the nuclei stain intensely.

Healing takes place rapidly; if the patient survives 10 days, it is likely that the areas will be completely reëpithelized. Casts are the most characteristic and outstanding microscopic findings; they are usually of two kinds:

(1) Most conspicuous are the pigmented masses of heme substances which are found inspissated within the lumen of the lower portions of the nephrons. These are particularly highly developed when there is destruction of muscle and apparently have their origin from myohemoglobin or some of its derivatives. In hemolytic conditions, such as transfusion reactions, hemoglobin casts develop which are similar to the myoglobin casts following destruction of muscle. In unstained sections the casts have a reddish hue; when stained with hematoxylin and eosin, they are usually brownish or copper-colored, but the reaction for iron is negative.<sup>61</sup> The casts have a smooth and solid appearance and occasionally assume the form of spherules. They tend to accumulate in greatest numbers in the distal convoluted tubules but are larger in the wider collecting tubules. When they occur near thin-walled veins, they are apt to be prominent.

(2) Less conspicuous are those casts which are not pigmented and have the appearance of hyalin casts. They are stained faintly with eosin and look much like inspissated and coagulated protein material. Tending to occur in the region of the lower nephron where the injury is most severe, they give the impression of obstructing and blocking the flow of urine through the nephron.

Another interesting aspect of the microscopic pathologic changes is that seen in the interstitial tissues around the foci in the tubules showing extreme disintegration. Edema and inflammatory reactions are evident. There is an accumulation of inflammatory cells, particularly lymphocytes and histiocytes, whereas granulocytes are scanty and giant cells are rarely seen. Fibrosis usually develops at the end of a week, and if there is a great deal of destruction, scars appear. These areas may vary from relatively few to large numbers, depending upon the severity of the reaction. The interstitial changes are particularly pronounced in the boundary zone and at times in the cortex around the venous channels near the glomeruli. If necrosis is severe, casts are extruded into the stroma, producing local reactions. As stated previously, one of the interesting pathologic changes is found in the region of the large venous channel, especially in the boundary zone. There the veins are rather thin-walled and normally course near the renal tubules. When the tubules are damaged, the veins apparently bulge into the lumen.

red cells are suddenly hemolyzed. When pigments are liberated in large quantities and cannot be metabolized in usual fashion by the liver to be excreted in the bile, they are excreted by the kidneys.<sup>2, 5, 39, 60, 72, 75, 112</sup> The mechanism by which the pigments reach the lumen of tubules is not clear. There are differences of opinion about the passage of hemoglobin molecules through the glomerular membranes. Since the molecular weight of hemoglobin is 68,000 and that of serum albumin is 70,000, it is considered by many observers to be unlikely that hemoglobin is able to pass through the glomerular membranes any more easily than serum albumin. However, several hypotheses have been presented to explain the mechanism by which hemoglobin enters the lumen of the nephron. One is that a small amount leaks through the glomeruli; a second is that some of the hemoglobin is broken into small components and is excreted as such; and a third is that damage to the tubules and glomeruli increases the permeability of these membranes to hemoglobin. None of these ideas is supported by sufficient direct data. As pointed out by Kreützer and his associates,<sup>57</sup> who reviewed the data on the excretion of hemoglobin and myoglobin in the urine in a study of spontaneous myohemoglobinuria, little is known about the details.

Myoglobin has a molecular weight of 17,500, or is about one-fourth the size of the hemoglobin molecule, and it contains one iron atom instead of four. Because of the presence of iron, the benzidine or guaiac test for occult blood in the urine of patients with myoglobinuria is positive. The diagnosis of myohemoglobinuria should be considered if the urine is dark and yields a positive test for occult blood, is free from red cells, and if no evidences of hemolytic disease exist. Since a minimum of about 20 mg. of hemoglobin per 100 c.c. of plasma has to be reached in order to give a reddish tinge to the plasma and since myoglobin has a renal threshold of about 20 mg. per 100 c.c. whereas that of hemoglobin is 100 mg., the color of the plasma aids in differential diagnosis. Therefore, it is possible to rule out hemoglobinuria, if a sample taken just before the appearance of dark urine does not exhibit a reddish tinge. Of course, myoglobin can be differentiated from hemoglobin and identified easily by means of ultracentrifugation, ultrafiltration and by spectroscopic examination. Myoglobinuria might be confused with acute porphyrinuria, but this is relatively unlikely since the porphyrins do not give a positive reaction to the benzidine or guaiac tests for occult blood. However, such problems are not troublesome in the presence of the lower nephron syndrome, since the other phases of the disease are distinct. The small size of the myoglobin molecule, the low renal threshold, and the rapid liberation of myoglobin from damaged muscle all contribute to the sudden overloading of the kidneys whenever there is crushing or damage to large masses of muscle. Apparently the low renal threshold is related to the molecular size of 17,500, which is small enough to permit passage through an unaltered glomerular membrane.

The heme compounds are apparently concentrated or precipitated in the lower part of the nephron. This is true of that derived from hemoglobin

the kidney. It has also been suggested that *organic* and *inorganic substances*, such as uric acid, phosphoric acid, potassium and creatine, liberated by injured tissue or toxic states, contribute to the renal damage.<sup>9, 35, 50, 61, 64, 96</sup>

Still others have suggested that *proteolytic enzymes* liberated in injured tissue may be responsible for the damage to the renal tubules.<sup>76</sup> Associated vomiting, disturbances in electrolyte balance, malnutrition, and dehydration may contribute to the intoxication and damage of the kidneys.<sup>15, 16, 61</sup> Disturbances in blood volume and in fluid balance could conceivably contribute to reduction in renal function, although such ideas remain conjectural.

It has also been proposed that disturbances in renal blood flow, particularly in the presence of shock, are of paramount importance in diminishing renal function and in damaging the nephron.<sup>26, 32, 54, 59, 81, 88, 93, 98, 99, 102, 103</sup> It has been observed that in patients suffering from shock, particularly if it is severe and prolonged, more severe damage to the tubules is sustained. This, however, may not be directly related to the shock, the latter being only another manifestation of the severity of the general injury. It is likely that all of the facts mentioned play some rôle, though the exact mechanism and the contributing rôle of each individual factor is not yet clear.

The mechanism by which oliguria develops is likewise unknown. Several hypotheses have been presented: (1) That it is due to a disturbance in glomerular filtration, which is the result of impairment of renal circulation.<sup>4, 29, 37, 40, 53, 67, 71, 85, 91, 92, 95</sup> This is related to the idea advanced by Trueta and his associates<sup>100</sup> of "shunting" of the renal circulation from the cortical portion of the kidneys to the medulla. It may be partially attributable to peripheral circulatory collapse and shock which impair glomerular filtration. (2) That oliguria results from tubular obstruction, which interferes with the rate of urinary flow. However, more and more observers are rejecting this concept. (3) That oliguria is incident to the disturbance in tubular reabsorption as a result of tubular damage from an impairment of renal circulation, a theory proposed by Phillips and coworkers<sup>53, 85</sup> and by others. The damaged areas, that is, the lower tubular portions of the nephron, become essentially parchment paper as far as selectivity of reabsorption is concerned.<sup>15, 16, 53, 61, 85</sup> Since there is no selective reabsorption, absorption of glomerular filtrate is complete qualitatively and almost quantitatively.<sup>87</sup> Consequently, the glomerular filtrate passes down the tubules and diffuses unaltered back into the circulation, so that there is almost complete reabsorption of the glomerular filtrate in its native state. This results in the formation of urine with approximately the same specific gravity as that of the glomerular filtrate, a value of 1.010. Lucké<sup>61</sup> and others are of the opinion that this almost complete leaking of glomerular filtrate through damaged tubular walls back into circulation is the best hypothesis to explain the histologic and clinical data of the lower nephron syndrome.

There are also many extrarenal factors concerned with the toxic picture. For example, anuria and azotemia will produce intoxication. Vomiting,

striction does not selectively involve the cortical portions of the kidney. When shock progresses so that the blood pressure reaches extremely low values, the filtration pressure is decreased and the quantity of glomerular filtrate becomes reduced. Corcoran, Taylor and Page<sup>36</sup> found a decrease in renal blood flow due almost entirely to an increase in renal vascular resistance in dogs following release of the tourniquets in "tourniquet-produced" shock. This is brought about by the increase in blood viscosity and by vasoconstriction of the afferent and efferent glomerular arterioles. Pain is of little influence, as blocking of sympathetic nerves has no effect upon renal function. Apparently, therefore, vasoconstriction is humoral in origin.

Phillips and his associates<sup>53, 55</sup> have shown that ischemia produced by gently clamping the renal arteries will interfere especially with tubular function. The main effect is to decrease selective absorption of the tubules so that glomerular filtrate is absorbed almost completely, the tubules becoming essentially parchment membranes, instead of living membranes with ability to absorb selectively. Similar observations have been made by Badenoch and Darmady.<sup>4</sup> These latter authors were able to produce disturbances in the distal segments, including patchy necrosis similar to that described by Bywaters<sup>15</sup> and Lucké.<sup>61</sup> Apparently, there was correlation between the histologic picture and disturbances in renal function.

*Sequelae.* The fatality rate is extremely high, the survival rate varying between 10 and 33 per cent. As far as is known, those who survive apparently do not experience residual disturbances in renal function, although it is not clear from published reports whether or not adequate follow-up studies have been conducted. A prolonged follow-up period would be required to ascertain the residual renal state. It is well to bear in mind when estimating morbidity that patients with the most severe damage die whereas those with the least survive; therefore, a follow-up of renal function would necessarily include only those with mild damage. With improvement in therapeutic methods, increased survival rate of the more seriously ill patient will result, thus permitting better evaluation of the problem of morbidity, particularly if follow-up studies are emphasized.

### TREATMENT

Before a discussion is undertaken of the management of the patient in whom the syndrome has developed, it is necessary to point out that there are certain types of the lower nephron syndrome which can be readily prevented. Most transfusion reactions are avoidable, being due entirely to carelessness. The same is true of intoxications, especially sulfonamides; more care in the selection of patients and during administration should reduce the incidence of injury from sulfonamides. Furthermore, when the slightest evidence of damage appears, immediate discontinuance of these drugs will usually result in minimal injury. It is the neglected patients who sustain the greatest damage. Uteroplacental damage with the complicating lower nephron syn-



The rôle of sympathetic blocking or sympathectomy is yet to be evaluated. Amputation should be performed if the part is definitely useless but unless it is done within the first 24 hours, postponement may be necessary, particularly if renal damage is serious.<sup>16</sup> Under such conditions, splinting and physical therapy should be employed until amputation can be performed.

Once renal failure, with oliguria and progressive uremia, develops, relatively little can be done except for the use of some of the more experimental procedures now under investigation, such as the artificial kidney or dialysis. It has been suggested that fluids should be administered to these patients in the presence of anuria and oliguria. However, it is well to remember that large quantities of fluids may produce severe edema and increase the damage. Sodium lactate, 5 per cent glucose, and sodium chloride may be used in amounts governed as much as possible by studies of the blood chemistry and by the clinical state. Human Ringer's solution may also be used. It is possible to administer fluids by means of gastric or duodenal tubes if the patient is not vomiting excessively; otherwise, intravenous medication must be employed. Fluids should not be administered to any extent beyond that which produces slight edema; in these amounts fluids might dilute the toxins and at the same time produce diuresis once renal function begins. Mercurial diuretics and decapsulation have been advocated, but it is unlikely that the latter is of any value. If results are not obtained promptly with mercurial diuretics, they should be discontinued. However, in view of the nature of the lesions and the mechanism of action of mercurials, it is likewise unlikely that these would be of great value—in fact, actual increased damage might result. One or two doses will probably be accompanied by no deleterious effects.

*The Artificial Kidney.* There has been increased interest in the use of artificial methods for eliminating metabolites. These procedures are based upon the principle that a method, even if crude, which would eliminate toxic substances during acute renal failure might prolong life long enough to permit renal repair and return of renal function. This idea is not a new one; it was advocated as early as 1923.<sup>44, 52, 79</sup> A number of papers have been published suggesting this procedure or peritoneal lavage: that of Ganter<sup>44</sup> in 1923, Landsberg and Gnoinski<sup>58</sup> in 1925, Rosenak and Siwon<sup>90</sup> in 1926, Bliss, Kastler and Nadler<sup>11</sup> in 1932, Haam and Fine<sup>51</sup> in 1932, Rhoads<sup>80</sup> in 1938, Balazs and his associates<sup>6</sup> in 1934, Wear, Sisk and Trinkle<sup>106</sup> in 1938, Fine, Frank and Seligman<sup>40</sup> in 1946, Buckley and Scholten<sup>13</sup> in 1947, and Basset and coworkers<sup>7</sup> in 1947.

The method of peritoneal lavage consists in placing a catheter in an upper lateral abdominal quadrant and another in the lower contralateral abdominal quadrant and running a large quantity of a modified Tyrode's solution through the peritoneal cavity. This is done continuously, 18 to 24 liters being used in 24 or 48 hours. The formulae for these solutions may be found in the aforementioned papers describing the technic. These solutions have sulfadiazine, heparin, and penicillin added in order to prevent

triple-bore, thin-walled rubber tube with a small balloon at its tip. In experimental animals, the tube was passed various distances down the intestinal tract, the balloon was inflated and the intestinal tract was irrigated with the perfusion fluid. Warm physiologic saline solution was used. The observers were able to reduce azotemia from 198 to 126, from 198 to 112, from 231 to 145 mg. per 100 c.c. in separate animals, using 12 to 18 liters of fluid over a period of about six hours. They found that the return rinsing fluid contained from 4.3 to 5.4 gm. of nonprotein nitrogen. This idea is essentially the same as gastric lavage but should be more promising because of the more rapid diffusion of materials and greater diffusion areas. Further investigations are definitely indicated.

As indicated by all investigators, if the patient survives the period of acute uremia and the acute disease so that repair may take place, diuresis would be established in many severely injured patients. The percentage of patients who sustain serious damage and who will again produce urine is undetermined. There must be some limit to the degree of damage and the ability for repair. Postmortem studies have indicated that if some of the patients had been able to survive a few more days, it is likely that renal function would have returned to normal. The therapeutic problem is to prolong life during a brief critical period. General hospitals with proper laboratory facilities and trained personnel should be prepared to employ the new procedures previously described, which promise to be life saving.

*General Therapeutic Measures.* It is important to remember that certain general measures must be emphasized in the management of these patients. Most important of all is *good nursing*. The patient should have constant attention, particularly when he is having his greatest difficulty. He should be made mentally as well as physically comfortable, since he is apt to become apprehensive and anxious about his disease. Most patients know they are seriously ill and are aware of the fact that they are likely to die.

Attention to electrolyte balance, fluids, vitamins, and nutrition should be emphasized. If possible, a large portion of the necessary fluids and carbohydrates should be given by gastric or duodenal tube. Protein intake should be held to a minimum during the time of renal failure, for the metabolism of administered proteins will only increase the rate of accumulation of non-protein nitrogen and toxic protein substances.

Borst<sup>12</sup> has found that a diet low or absent in protein, consisting almost entirely of fat and carbohydrate, is of considerable value in the management of acute renal insufficiency. Some of his patients were fed a diet consisting of 150 gm. of butter and 200 gm. of sugar, a total of 2,000 calories. This yields practically no protein and little potassium and phosphorus. Patients have received this diet for over three consecutive weeks, except for variations in quantity, without difficulty and with great benefit during periods of uremia. Contrary to most opinions, severe-to-complete restriction of proteins in the diet reduces protein catabolism to extremely low levels, so that by the end of three days the daily nitrogen excretion is less than 6 gm., and

15. BYWATERS, E. G. L.: War medicine series; crushing injury, *Brit. Med. Jr.*, 1942, ii, 643-646.
16. BYWATERS, E. G. L.: Ischemic muscle necroses; crushing injury, traumatic edema, the crush syndrome, traumatic anuria, compression syndrome: a type of injury seen in air raid casualties following burial beneath debris, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 1103-1109.
17. BYWATERS, E. G. L., and BEALL, D.: Crush injuries with impairment of renal function, *Brit. Med. Jr.*, 1941, i, 427-432.
18. BYWATERS, E. G. L., DELORY, G. E., RIMINGTON, CLAUDE, and SMILES, JOHN: Myohemoglobin in the urine of air raid casualties with crushing injury, *Biochem. Jr.*, 1941, xxxv, 1164-1168.
19. BYWATERS, E. G. L., and DIBLE, J. H.: Renal lesion in traumatic anuria, *Jr. Path. and Bact.*, 1942, liv, 111-120.
20. BYWATERS, E. G. L., and DIBLE, J. H.: Acute paralytic myohaemoglobinuria in man, *Jr. Path. and Bact.*, 1943, lv, 7-15.
21. BYWATERS, E. G. L., and STEAD, J. K.: Production of renal failure following injection of solutions containing myohaemoglobin, *Quart. Jr. Exper. Physiol.*, 1944, xxxiii, 53-70.
22. BYWATERS, E. G. L., and others: Discussion on the effects on the kidney of trauma to parts other than the urinary tract, including crush syndrome, *Proc. Roy. Soc. Med.*, 1942, xxxv, 321-339.
23. COLMERS, DR.: Ueber die durch das Erdbeben in Messina am verursachten Verletzungen, *Arch. f. klin. Chir.*, 1909, xc, 701-747.
24. CORCORAN, A. C., and PAGE, I. H.: Effects of hypotension due to hemorrhage and of blood transfusion on renal function in dogs, *Jr. Exper. Med.*, 1943, lxxviii, 205-224.
25. CORCORAN, A. C., and PAGE, I. H.: Renal damage from ferroheme pigments, myoglobin, hemoglobin, hematin, *Texas Rep. Biol. and Med.*, 1945, iii, 528-544.
26. CORCORAN, A. C., TAYLOR, R. D., and PAGE, I. H.: Immediate effects on renal function of the onset of shock due to partially occluding limb tourniquets, *Ann. Surg.*, 1944, cxviii, 871-886.
27. DAMON, S. R.: Food infections and food intoxications, 1928, Williams and Wilkins Co., Baltimore.
28. DANIELS, W. B., LEONARD, B. W., and HOLTZMAN, S.: Renal insufficiency following transfusion; report of 13 cases, *Jr. Am. Med. Assoc.*, 1941, cxvi, 1208-1215.
29. DARMADY, E. M.: Renal anoxia and the traumatic uraemia syndrome, *Brit. Jr. Surg.*, 1947, xxxiv, 262-271.
30. DARMADY, E. M., SIDONS, A. H. M., CORSON, T. C., LANGTON, C. D., VITEK, Z., BADENOCH, A. W., and SCOTT, J. C.: Traumatic uraemia, reports on 8 cases, *Lancet*, 1944, ii, 809-812.
31. DEGOWIN, E. L., WARNER, E. D., and RANDALL, W. L.: Renal insufficiency from blood transfusion; anatomic changes in man compared with those in dogs with experimental hemoglobinuria, *Arch. Int. Med.*, 1938, lxi, 609-630.
32. DOLE, V. P., EMERSON, J., JR., PHILLIPS, R. A., HAMILTON, P., and VAN SLYKE, D. D.: The renal extraction of oxygen in experimental shock, *Am. Jr. Physiol.*, 1946, cxlv, 337-345.
33. DOUGLAS, J. W. B.: Incidence of signs of renal injury following prolonged burial under debris in an unselected series of 764 air-raid casualties admitted to hospital, *Brit. Jr. Urol.*, 1945, xvii, 142-147.
34. DUNN, J. S., HAWORTH, A., and JONES, N. A.: Pathology of oxalate nephritis, *Jr. Path. and Bact.*, 1924, xxvii, 299-318.
35. DUNN, J. S., and POLSON, C. J.: Experimental uric acid nephritis, *Jr. Path. and Bact.*, 1926, xxix, 337-352.
36. EDWARDS, J. G.: The renal tubule (nephron) as affected by mercury, *Am. Jr. Path.*, 1942, xviii, 1011-1027.

60. LOUW, ASGER, and NIELSEN, HOLGER E.: Paroxysmal paralytic hemoglobinuria, *Acta med. Scandinav.*, 1944, cxvii, 424-436.
61. LUCKÉ, B.: Lower nephron nephrosis, *Mil. Surg.*, 1946, xcix, 371-396.
62. LUETSCHER, J. A., JR., and BLACKMAN, S. S., JR.: Severe injury to kidneys and brain following sulfathiazole administration; high serum sodium and chloride levels and persistent cerebral damage, *Ann. Int. Med.*, 1943, xviii, 741-756.
63. LUND, C. C., GREEN, R. W., TAYLOR, F. H. L., and LEVENSON, S. M.: Burns, collective review, *Internat. Abstr. Surg.*, 1946, lxxxii, 443-478, in *Surg., Gynec. and Obst.* (June) 1946.
64. McFARLANE, D.: Experimental phosphate nephritis in rat, *Jr. Path. and Bact.*, 1941, lii, 17-24.
65. McLEITCH, N. G. B.: Renal lesions in case of excessive vomiting, *Jr. Path. and Bact.*, 1943, lv, 17-22.
66. MAEGRAITH, B. G., and FINDLAY, G. M.: Oliguria in blackwater fever, *Lancet*, 1944, ii, 403-404.
67. MAEGRAITH, B. G., HARVARD, R. E., and PARSONS, D. S.: Renal syndrome of wide distribution induced possibly by renal anoxia, *Lancet*, 1945, ii, 293-296.
68. MALAMUD, N., HAYMAKER, W., and CUSTER, R. P.: Heat stroke; clinicopathologic study of 125 fatal cases, *Mil. Surg.*, 1946, v, 397-449.
69. MALLORY, T. B.: Hemoglobinuric nephrosis in traumatic shock, *Am. Jr. Clin. Path.*, 1947, xvii, 427-443.
70. MANN, F. C.: Peripheral origin of surgical shock, *Bull. Johns Hopkins Hosp.*, 1914, xxv, 205-212.
71. MARSHALL, E. K., JR., and CRANE, M. M.: The influence of temporary closure of the renal artery on the amount and composition of the urine, *Am. Jr. Physiol.*, 1923, lxiv, 387-403.
72. MASON, J. B., and MANN, F. C.: Effect of hemoglobin on volume of kidney, *Am. Jr. Physiol.*, 1931, xcvi, 181-185.
73. MILLIKAN, G. A.: Muscle hemoglobin, *Physiol. Rev.*, 1939, xix, 503-523.
74. MINAMI AUS TOKIO, DR. SEIGO: Über Nierenveränderungen nach Verschüttung, *Virchow's Arch. f. path. Anat.*, 1923, ccxlv, 247-267.
75. MINETT, F. C.: Haemoglobinurias and myoglobinurias of animals, *Proc. Roy. Soc. Med.*, 1935, xxviii, 672-678.
76. MIRSKY, I. A., and FREIS, E. D.: Renal and hepatic injury in trypsin "shock," *Proc. Soc. Exper. Biol. and Med.*, 1944, lvii, 278-279.
77. MURPHY, F. D., KUZMA, J. F., POLLEY, T. Z., and GRILL, J.: Clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, *Arch. Int. Med.*, 1944, lxxiii, 433-443.
78. MURRAY, GORDON, DELORME, EDMUND, and THOMAS, NEWELL: The artificial kidney, *Jr. Am. Med. Assoc.*, 1948, cxxxvii, 1596-1599.
79. NECHELES, HEINRICH: Über Dialysieren des Stromenden Blutes am Lebenden, *Klin. Wchnschr.*, 1923, ii, 1257.
80. OLIVER, JEAN: When seeing is believing, *Stanford Med. Bull.*, 1948, vi, 7-12.
81. OLSON, W. H., WALKER, L., and NECHELES, H.: Study of anuria in experimental shock, *Proc. Soc. Exper. Biol. and Med.*, 1944, lvi, 64-67.
82. PAGE, I. H.: Occurrence of vasoconstrictor substance in blood during shock induced by trauma, hemorrhage and burns, *Am. Jr. Physiol.*, 1943, cxxxix, 386-398.
83. PAGE, I. H., and ABELL, R. G.: State of vessels of mesentery in shock produced by constricting limbs and behavior of vessels following hemorrhage, *Jr. Exper. Med.*, 1943, xxvii, 215-232.
84. PAXSON, N. F., GOLUB, L. J., and HUNTER, R. M.: Crush syndrome in obstetrics and gynecology, *Jr. Am. Med. Assoc.*, 1946, cxxxi, 500-504.
85. PHILLIPS, R. A., and HAMILTON, P. B.: Effect of 20, 60 and 120 minutes of renal ischemia on glomerular and tubular function, *Am. Jr. Physiol.*, 1948, clii, 523-530.

# NECROSIS OF RENAL PAPILLAE\*

By EDWARD D. ROBBINS, M.D., *Chicago, Illinois*, and ALFRED ANGRIST, M.D., *Long Island, New York*

## INTRODUCTION

NECROSIS of the renal papillae is a curious and striking lesion which most pathologists meet only occasionally at the autopsy table. The purpose of this presentation is to report briefly the cases of this disease seen at the Queens General Hospital, to discuss some of the theories of its pathogenesis, and more particularly, to relate this lesion to a similar one produced in the experimental animal by a dietary deficiency of certain fatty acids.

*Necrosis of Renal Papillae in Man.* The literature concerning this lesion, which is variously known as renal papillitis, medullary necrosis, papillitis necroticans, necrotizing renal papillitis, etc. has recently been reviewed in detail by Edmondson, Martin, and Evans.<sup>1</sup> These authors have traced the first case report back to 1877, but Günther<sup>2</sup> in 1937 first emphasized the frequent association of diabetes with this lesion.

Approximately 110 cases were reported in the literature up to 1947,<sup>1, 4, 5</sup> and of these, 62 had diabetes and 48 did not; of the latter, 85 per cent had urinary tract obstruction. From the large series reported by Edmondson et al.<sup>1</sup> and by Robbins, S. L., Mallory and Kinney,<sup>5</sup> it is apparent that 12 to 20 per cent of diabetics coming to autopsy have acute pyelonephritis. Of these, 25 per cent have necrosis of the papillae. Hence the lesion may be found in 3.2 to 5 per cent of all diabetics. In contrast, 3.3 per cent of non-diabetics coming to autopsy have acute pyelonephritis. Of these, 2 per cent have necrosis of the papillae. Hence the lesion may be found in only 0.06 per cent of non-diabetics. The overall incidence of the disease in pyelonephritis is about 4 per cent.<sup>1</sup> Robbins, Mallory and Kinney found that in 74 per cent of their cases, death was attributable directly to the papillary necrosis.

The great majority of non-diabetics who have papillary necrosis have some obstruction of the urinary tract. This was present in six out of seven cases in one series,<sup>5</sup> in 20 out of 21 cases<sup>1</sup> in another; and in five out of six of our cases. Benign hypertrophy of the prostate is the usual cause, but carcinoma of the prostate, urethral stricture, "cord" bladder and renal calculi have also been found.

The variation in sex incidence is also striking. In diabetics, the ratio of females to males is 2:1; in non-diabetics the ratio of females to males is 1:6, due to greater frequency of urinary tract obstruction in males, chiefly

\* Received for publication October 14, 1948.

The Transactions of the New York Pathological Society contain an abstract of this paper, together with discussion.

was virtually fat-free. This diet consisted of sucrose, casein which was carefully purified and rendered fat free by ether extraction, McCallum's salt mixture, ether extracted yeast for the vitamin B complex, the non-saponifiable matter from cod liver oil for vitamins A and D, and in later experiments the non-saponifiable matter from wheat germ oil for vitamin E.

Rats fed such a diet from the day of weaning develop (1) a lesion of the tail characterized by scaliness, inflammation, swelling, and later necrosis of the tip, (2) redness, swelling and scaliness of the feet, (3) dandruff and loss of body hair, (4) cessation of growth, (5) bloody urine. The animals maintained a plateau of the weight curve for weeks and months, then declined in weight and died. At autopsy, five of the eight animals had abnormal kidneys. It was felt that the immediate cause of death was kidney degeneration.

The addition of 10 drops of lard daily to the diet of these diseased animals produced a prompt cure of all lesions and a gain in weight; while the addition of 2 per cent of the total diet as lard from the beginning of the experiment completely protected the animal from the disease. Furthermore, the addition of pure glycerol, or the non-saponifiable matter from lard did not protect against the disease, but 13 drops of the fatty acid fraction from lard did give protection. Feeding 200 mg. per day of the fatty acid fraction of lard to a diseased rat on the fat free diet produced a 2 gram/day increase in weight, a tenfold effect.

They demonstrated by a series of experiments that (1) the disease is not due to a deficiency of vitamins A, B, D or E; (2) the fat free yeast, and the non-saponifiable matter from cod liver oil, and from wheat germ oil, were adequate sources of these vitamins and that (3) these latter substances were absorbed in the absence of fat in the diet. By feeding oils of various composition with regard to saturated and unsaturated fatty acids, it was shown that cures could only be effected by unsaturated fatty acids, and of these, only linoleic or acids of higher unsaturation. Oleic acid, and saturated fatty acids were without effect. The authors concluded that warm blooded animals cannot synthesize appreciable quantities of linoleic acid, or more unsaturated fatty acids.

Later experiments<sup>8</sup> demonstrated that (1) the respiratory quotient of rats with the fat deficiency disease rises above unity after carbohydrate feeding, indicating the formation of fat from carbohydrate, but the persistence of the disease proves that linoleic or other more unsaturated fatty acids are not formed.<sup>9</sup> (2) The highly unsaturated fatty acids of cod liver oil can be used by fat deficient rats for growth, but the skin lesions can only be cured by linoleic or linolenic acids, which are lacking in cod liver oil.<sup>10</sup> (3) Feeding pure fatty acids as the methyl esters proves again the complete ineffectiveness of oleic acid, the curative value of linoleic and linolenic acids, and the ineffectiveness of alpha eleostearic acid, an isomer of linolenic acid.<sup>11</sup> (4) The scaly skin and tail necrosis in this disease are not a symptom com-

with fat deficiency disease, in which cures were attempted with various inadequate fats, the same changes were noted as above. However, calcification of the papilla and apical necrosis were present in one rat of nine. In a group of rats in whom the deficiency disease was first induced, and then cured by the addition of lard to the diet, the kidneys were normal grossly and microscopically. Another group of 35 rats with the fat deficiency disease was treated with various fats including linseed oil, corn oil, olive oil, etc. At autopsy, the general condition was fair to good, the animals being only 10 per cent underweight on an average. However, degenerative changes and calcification of cortical tubule cells were widespread. Degeneration of papillary ducts was found in 21 cases, with calcification and necrosis of the papillae in seven of the 21. The necrotic areas were smaller than those found in the first group.

Thirty-eight rats, which were fed diets containing lard, or a regular stock diet, were used as the controls.

These authors concluded that characteristic renal lesions were present in rats fed on a diet free of fat but otherwise adequate. The most striking lesion was calcification of tubules and necrotic areas in the renal medulla, with disintegration of the apex of the pyramid in some. The addition of lard to the diet prevented the renal lesion, or cured it to a large extent.

### MATERIAL

Fourteen cases of papillary necrosis which were autopsied at the Queens General Hospital, are described below. These include 13 acute cases, and one which was healed. Eight of these cases were diabetics and six non-diabetics.

### DIABETIC CASES

Seven acute cases, and one with healed papillitis were found in diabetics. (The latter will be discussed separately.) There were six females, and two males, in an age range from 42 to 79 years, with an average age of 57. Two patients were admitted to the hospital in coma, and one was stuporous. Three patients died in 18 hours or less after entering the hospital. Two of these had 3 to 4 plus glycosuria, but no acetone; yet both were thought to be in diabetic coma. The shortest total duration of illness from the first symptoms was 3.5 days. The urine was abnormal in all the acute cases, though only three were noted to have pyuria. In the three acute cases in which blood urea levels were done, all had marked azotemia. In the four cases in which the hemoglobin was reported, it varied from 8.5 to 10.5 grams, with red cell counts between 3 and 3.5 million. Three had unilateral papillary necrosis, and two showed unilateral pyelonephritis.

The single male patient in the acute cases had benign prostatic hypertrophy with urinary retention and a cystotomy was performed during his hospital course.

At autopsy, the kidneys contained multiple cortical abscesses, with a perirenal abscess on the left. Necrosis of the papillae was present in the left kidney. The pelves and ureters were dilated and revealed ecchymoses. There was a bullous hemorrhagic cystitis. Microscopy revealed advanced papillary necrosis (figures 1 and 2).

*Case 2.* This 57 year old Negro female was admitted in coma. The past history was not known, but she was reported to have been "sick" for eight days. On physi-



FIG. 2. Micro-photograph showing junction zones between necrotic tissue of papilla and viable tissue with inflammatory reaction in between.

cal examination, she was in deep coma, dehydrated, hyperpneic, and had an acetone odor on the breath. Temperature 102°.

Laboratory data: Urine: milky; glucose 4 plus, acetone 3 plus; loaded with pus cells and pus casts. Six hours later, after she had received 725 units of insulin, three liters of Hartman's solution, and intravenous sulfadiazine, the glycosuria fell to 1 plus, the acetonuria disappeared, and she showed signs of returning consciousness. She



Laboratory data: Urine: Albumin 3 plus; glucose 2 plus; microscopically negative; Hb. 9.5 gm.; red blood cells 3.29 millions; white blood cells 7650. Blood sugar 315 mg. per cent.

She developed an abscess of the buttock, which was incised and drained. She ran a spiking temperature, deteriorated rapidly, and died on the eleventh post operative day (the fifty-first hospital day).

Clinical diagnosis: Diabetes mellitus; arteriosclerotic heart disease; abscess of buttocks; bronchopneumonia.

At autopsy, the kidneys were large, pale, and contained many cortical abscesses. There was bilateral renal papillitis, bilateral ureteritis, and cystitis. Microscopy showed circumscribed areas of typical necrosis of the renal papillae.

Case 6. This 43 year old, white female had fractured the right hip 10 weeks previously. After three weeks at another hospital, she was sent home where she began to vomit continuously for the next two weeks. For the past 12 days the urine had been bloody, and there had been a bloody stool on the day of admission. The past history included treatment for lues and known diabetes for 14 years.

Physical examination revealed a stuporous pale patient, with Argyll-Robertson pupils, absent knee and ankle jerks; and blood pressure 80 mm. Hg systolic and 60 mm. diastolic.

Laboratory data: Urine—albumin 2 +, glucose 0, acetone 0, micro-clumps of pus cells and many red blood cells. Hemoglobin 8 gm., white blood cells 15,200 with 88 per cent polynuclears. Blood urea 170 mg. per cent. Blood sugar 140 mg. per cent.

Cystoscopy revealed a necrotizing cystitis with involvement of the trigone. The blood urea fell to 85 mg. per cent but CO<sub>2</sub> combining power was found to be 33 vol. per cent. Culture of the bladder: *B. coli* and *Streptococcus non-hemolyticus*. The white blood count rose to 30,700 with 89 per cent polynuclears. The urines were maintained sugar free. She died on the tenth hospital day.

Clinical Diagnosis: Diabetes mellitus; necrotizing cystitis; acute pyelonephritis.

At autopsy the kidneys were large and smooth. All the renal papillae showed yellowish necrosis. There was an acute ureteritis and a severe hemorrhagic cystitis. Microscopy revealed an advanced papillary necrosis.

Case 7. This 52 year old white female was admitted with a six hour history of aphasia and weakness of the legs. She had complained of being "sick" for the previous three days but the nature of her complaints was not known. She had complained of headaches, dizziness and nocturia for the past year.

Physical examination revealed an obese, aphasic patient with a temperature of 99.2°. There was no paralysis of the extremities, but the left naso-labial fold was flattened. The plantar reflexes were normal.

Laboratory data: Urine—glucose 4 plus, acetone 0, no casts, microscopically negative.

Her temperature rose rapidly to 105.4°. She died 17 hours after admission.

Clinical diagnosis: Cerebrovascular accident; diabetes mellitus.

At autopsy the papillae of both kidneys were necrotic. The pelves were injected; the ureters and bladder were unremarkable. There were no areas of hemorrhage or softening in the brain. On microscopy the necrosis of the papillae was advanced.

Case 8. This 79 year old white male was admitted from a convalescent home. One month previously his right leg had been amputated for gangrene. He was a known diabetic, regulated by diet alone. On admission he was pale and disoriented. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. The heart was enlarged. Basal râles were present in both lungs. The prostate was 3 plus enlarged, hard, nodular and non-tender. There was a right mid-thigh amputation stump.

Clinical diagnosis: Hypertensive and arteriosclerotic heart disease III C; diabetes mellitus; anemia.

At autopsy the left kidney was unremarkable except for a 2 cm. cortical adenoma. The right kidney was unremarkable except for the papillae, which were atrophic and fibrotic. The pelvis was not dilated. The ureters were patent. The bladder showed moderate trabeculation, but no evidence of inflammation. Microscopy revealed healed renal papillitis of the right kidney (figure 3).



FIG. 4. Note hydronephrosis resulting from absorption of necrotic papillae in the upper-most and lower-most calyces.

Case 8 with healed papillary necrosis, deserves special mention. He was an elderly diabetic who had had an amputation of the right leg one month before admission. The urine was negative and the blood urea nitrogen was not elevated. He died on the eleventh hospital day of a severe broncho-

benign hypertrophy and two carcinomas of the prostate). Four of the five had prostatic operations during their hospital stay. All had azotemia. All were moderately anemic, with hemoglobins ranging from 8.5 to 11 grams, and red cell counts from 3 to 4 million. Pyuria was found in four cases, and hematuria in four cases (two gross, two microscopic).

At autopsy all had extensive upper and lower urinary tract inflammatory disease, with cystitis, ureteritis and bilateral pyelonephritis. Only two of the six had advanced necrosis of the papillae—the others revealed limited areas of necrosis within the papillae in areas of acute pyelonephritis.

The lone female had striking bilateral advanced papillary necrosis, but only a moderate urinary tract infection. She had, in addition, a fractured skull, portal cirrhosis and jaundice. The urine was reported sugar free, but a blood sugar was found to be 186 mg. per cent so that this case may well belong to the diabetic group.

#### CASE REPORTS

*Case 1.* This 73 year old female fell at home and struck her head. One week later she developed nose bleeds, and jaundice, and was admitted to the hospital. The skin and sclerae were icteric. The liver was palpable one finger's-breadth below the costal margin. Roentgenograms of the skull revealed a fracture in the mastoid region probably extending to the base.

Laboratory data: Urine: albumin 2+, glucose 0, 12 red blood cells per high power field, and 10 white blood cells per high power field. There were no clumps or casts. Hemoglobin 10.5 gm.; red blood cells 3.4 millions; white blood cells 31,100 with 87 per cent polynuclears. Non-protein nitrogen 162 mg. per cent. Blood sugar 186 mg. per cent.

She became comatose, incontinent, and developed projectile vomiting and tarry stools. Her temperature varied from 99° to 101°. She died on the seventh hospital day.

At autopsy the kidneys revealed advanced bilateral papillary necrosis. The microscopic sections demonstrated the classical histology of advanced papillary necrosis (figure 6).

*Case 2.* This 74 year old white male entered the hospital because of difficulty in urinating during the preceding month. Two weeks before admission he had complete retention and was catheterized on several occasions. On rectal examination, the prostate was enlarged (grade 2), but not hard.

Laboratory data: Urine on admission—albumin 2 plus, glucose 0, microscopically negative. Later specimens were grossly bloody, and contained pus cells. Hemoglobin 8.5 gm., red blood cells 3.1 millions. The blood urea was 15 mg. per cent.

A one stage perineal prostatectomy was performed. Three weeks after operation, necrosis of the anterior rectal wall and the operative site occurred. His condition deteriorated, the blood urea rose to 50 mg. per cent, and he died on the fiftieth hospital day.

Clinical diagnosis: Post-operative perineal prostatectomy with necrosis of anterior rectal wall, sepsis and anemia; arteriosclerotic heart disease.

At autopsy there was a marked bilateral suppurative pyelonephritis, an acute ureteritis, and a hemorrhagic cystitis. On microscopic section the renal papillae showed small circumscribed areas of necrosis of characteristic form.

*Case 3.* A 78 year old white male entered the hospital with complaints of difficulty in urinating (frequency, nocturia, dysuria) for one month. Rectal examination revealed a fixed, irregular, hard prostate. Temperature 100.2°.

Clinical diagnosis: Benign prostatic hypertrophy; uremia.

At autopsy, bilateral suppurative pyelonephritis, with ureteritis and gangrenous cystitis, was disclosed. Microscopy revealed small areas of non-reactive central necrosis within the papillae.

*Case 5.* This 77 year old white male entered the hospital with the history of progressive swelling of both legs, which spread to involve the scrotum and abdomen. Dyspnea and orthopnea had been present for the preceding nine months. He had frequency and nocturia. There was no history of diabetes.

Physical examination: Blood pressure 130 mm. Hg systolic and 80 mm. diastolic. The heart was not enlarged, but was fibrillating. Ascites was present. The liver was palpable two fingers below the costal margin. There was 4 plus pitting sacral and leg edema.

Laboratory data: Urine—albumin 0, glucose 0, 40 red blood cells per high power field. Blood urea 29 mg. per cent, blood sugar 125 mg. per cent.

He developed urinary retention which required an indwelling catheter. A spiking fever developed. He was given sulfa drug in small doses. On the nineteenth hospital day sulfa crystalluria with many white blood cells and red blood cells was found. The blood urea rose to 31 mg. per cent. A cystotomy was performed. His condition improved, and he became ambulatory. The blood urea on the thirty-sixth hospital day was 17 mg. per cent. A trans-urethral resection was performed. Following this he developed a shaking chill. Plasma (200 c.c.) was given. The next day he was jaundiced. The blood urea rapidly rose to 65 mg. per cent and then to 124 mg. per cent with 13.6 mg. per cent creatinine. The icteric index was 50. He died on the forty-fifth hospital day.

At autopsy, the kidneys contained multiple abscesses in the cortex. Microscopic sections revealed small areas of necrosis within the papillae, with only marginal reaction.

*Case 6.* This 81 year old white male was admitted to the hospital because of urinary retention with overflow incontinence. He had had symptoms of prostatism for five years, which had become markedly aggravated within the previous two months (frequency, nocturia, weak stream, etc.).

Physical examination: The bladder was palpated up to the umbilicus. The prostate was 1 plus enlarged, but soft.

Laboratory data: First urine—grossly bloody, albumin 2 plus, glucose 0, blood urea 17 mg. per cent.

A two stage suprapubic prostatectomy was performed. He ran a febrile course. The urine continued to show 2 plus albumin, and white cells. Blood urea rose to 34 mg. per cent. He died on the fifty-second hospital day.

Clinical diagnosis: Benign hypertrophy of prostate; hydronephrosis; pyelonephritis.

Autopsy disclosed multiple cortical abscesses in the kidneys. Papillary necrosis was noted bilaterally. The microscopic sections revealed small areas of necrosis within the pyramids.

### THEORIES OF PATHOGENESIS

A variety of theoretical explanations of the pathogenesis of necrosis of the renal papilla has been advanced.

*I. The Rôle of Infection.* It is at once apparent that all of the cases occur in association with active pyelonephritis, which is usually suppurative. The toxins of bacteria,<sup>2</sup> the coagulase and necrosin of *Staphylococcus aureus*,<sup>1</sup> and the toxic metabolic products of *B. coli*<sup>18</sup> have all been suggested as factors in the production of the lesion. However, the multiplicity of the bac-

*III. Mechanical Factors.* Robbins, S. L., et al.<sup>5</sup> state that papillary ischemia best explains the occurrence of papillary necrosis. They suggest that the marked inflammatory reaction in the diabetics, and the back pressure of urinary tract obstruction, both operate to further mechanically reduce the anatomically inferior blood supply to the papillae by compression of the



FIG. 7. Micro-photograph showing para-amyloid-like hyalin material in the stroma of the papilla which in this instance bears no direct relationship to necrosis of papillae.

thin wall capillaries. Davson and Langley<sup>18</sup> also discuss the rôle of mechanical pressure, and question why, if pressure on blood vessels were the cause of the necrosis, the lesion is not more often seen in hydronephrosis or nephrolithiasis. Mellgren and Redell<sup>26</sup> consider the deposition of the "para-amyloid" in the interstitial tissue of the renal papillae to play a

of the pyramid with distal ischemic infarction, as described by Robbins, S. L., Mallory and Kinney.

Comparison with necrosis of the papillae produced by chemical poisons<sup>23, 24</sup> confirms the above interpretation, that the lesion is produced by death of tissue en masse, followed by a variable amount of reactive inflammation and bacterial proliferation. Certain specific chemical poisons have successfully produced papillary necrosis in the experimental animal. Levaditi<sup>23</sup> produced the lesion in rabbits, guinea pigs and mice by subacute poisoning with vinylamin. Rehns<sup>24</sup> produced the lesion in rabbits and guinea pigs, but not mice or rats, by administration of tetrahydroquinoline and its methyl esters. The mode of action of these chemicals, and their relation, if any, to fat metabolism, are unknown to us.

The experimental production of papillary necrosis in rats by a fat-free diet has been detailed earlier in this report. It was shown by Burr and co-workers that the deficiency is chiefly one of unsaturated long chain fatty acids; that a very small amount of these may restore normal fat metabolism; and that although the fat-deficient animals synthesize fat, they cannot synthesize the necessary long chain unsaturated fatty acids. It may be very significant that in diabetics there exists a profound disturbance in fat metabolism, with uncontrolled overproduction of fatty acids. The non-diabetics we have studied were all elderly men with chronic urinary tract obstruction and infection, with anemia and azotemia, all of which were additive in producing debility and malnutrition, with its accompanying disturbance of fat metabolism (e.g., "starvation acidosis"). E. M. Boyd<sup>27</sup> found that during fever neutral fat increases 50 per cent, but total and free cholesterol and phospholipids fall, after an initial rise. He noted that the iodine number of plasma fatty acids fell markedly after an initial rise.

It may be said, then, that disturbed fat metabolism is a common factor in diabetes; in non-diabetics with debility, malnutrition, and sepsis; and in the experimental animal on fat-free diet. It is not possible to say at this time whether a deficiency in unsaturated fatty acids plays a direct rôle in the pathogenesis of papillary necrosis, or whether it plays an indirect rôle by inducing alterations in renal hemodynamics, or in the responses to infection.

Although azotemia is commonly found in patients with this lesion, it cannot be the primary mechanism, for papillary necrosis is not commonly found in diseases that produce uremia most commonly, i.e., arteriolar nephrosclerosis, chronic glomerulonephritis, and chronic progressive pyelonephritis. Uremia and azotemia undoubtedly do play a significant part in the debility and malnutrition of these cases. Further, in diabetics, the illness may be fatal within a far shorter time than is found in uremia. It would seem that azotemia and uremia contribute to the lesion but are not its causes, and rather may be caused by it.

Papillary necrosis is not invariably fatal, for healing does occur, as is demonstrated in our case 8; in a case reported by Edmondson et al.<sup>1</sup>; and in

BIBLIOGRAPHY

1. EDMONDSON, H. A., MARTIN, H. E., and EVANS, N.: Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus, *Arch. Int. Med.*, 1947 lxxix, 148-175.
2. GÜNTHER, G. W.: Die Papillennekrosen der Niere bei Diabetes, *München. med. Wchnschr.*, 1937, lxxxiv, 1695-1699.
3. ALKEN, C. E.: Die Papillennekrose, *Ztschr. f. Urol.*, 1938, xxxii, 433-438.
4. PELLEGRIN, F. A.: Necrotizing renal papillitis, *Permanente Foundation Med. Bull.*, 1947, v, 66-74.
5. ROBBINS, S. L., MALLORY, G. K., and KINNEY, T. D.: Necrotizing renal papillitis: a form of acute pyelonephritis, *New England Jr. Med.*, 1946, ccxxxv, 885-893.
6. HARRISON, J. H., and BAILEY, O. T.: Significance of necrotizing pyelonephritis in diabetes mellitus, *Jr. Am. Med. Assoc.*, 1942, cxviii, 15-20.
7. BURR, G. O., and BURR, M. M.: New deficiency disease produced by rigid exclusion of fat from diet, *Jr. Biol. Chem.*, 1929, lxxxii, 345-367.
8. BURR, G. O., and BURR, M. M.: On the nature and rôle of fatty acids essential in nutrition, *Jr. Biol. Chem.*, 1930, lxxxvi, 587-621.
9. WESSON, L. G., and BURR, G. O.: Metabolic rate and respiratory quotients of rats on fat-deficient diet, *Jr. Biol. Chem.*, 1931, xci, 525-539.
10. BURR, G. O., BURR, M. M., and BROWN, W. R.: On nutritive value of certain oils, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 905-907.
11. BURR, G. O., BURR, M. M., and MILLER, E. S.: On fatty acids essential in nutrition, *Jr. Biol. Chem.*, 1932, xcvi, 1-9.
12. BURR, G. O., and BROWN, W. R.: On fatty acids essential in nutrition, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1349-1352.
13. HANSEN, A. E., and BURR, G. O.: Studies on iodine absorption of serum in rats fed on fat-free diets, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1200-1201.
14. HANSEN, A. E., and BURR, G. O.: Iodine numbers of serum lipids in rats fed on fat-free diets, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1201-1203.
15. BURR, G. O., and BEBER, A. J.: Metabolism studies with rats suffering from fat deficiency, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxi, 911-912.
16. BURR, G. O., BROWN, J. B., KASS, J. P., and LUNDBERG, W. O.: Comparative curative values of unsaturated fatty acids in fat deficiency, *Proc. Soc. Exper. Biol. and Med.*, 1940, xlv, 242-244.
17. BORLAND, V. G., and JACKSON, C. M.: Effects of fat-free diet on structure of kidney of rats, *Arch. Path.*, 1931, xi, 687-708.
18. DAVSON, J., and LANGLEY, F. A.: Papillitis renis necroticans, *Jr. Path. and Bact.*, 1944, lvi, 327-333.
19. SHEEHAN, H. L.: Medullary necrosis of kidneys, *Lancet*, 1937, ii, 187-189.
20. MENKIN, V.: Biochemical factors in inflammation and diabetes mellitus, *Arch. Path.*, 1942, xxxiv, 182-195.
21. MENKIN, V.: On mechanism of enhanced diabetes with inflammation, *Am. Jr. Physiol.*, 1941, cxxxiv, 517-541.
22. MALLORY, G. K., CRANE, A. R., and EDWARDS, J. E.: Pathology of acute and healed experimental pyelonephritis, *Arch. Path.*, 1940, xxx, 330-347.
23. LEVADITI, C.: Recherches expérimentales sur la nécrose de la papille rénale, *Arch. internat. de pharmacodyn. et de therap.*, 1901, viii, 45-63.
24. REHNS, J.: D'une nécrose typique de la papille rénale déterminée par la tétrahydroquinoléine et certains de ses dérivés, *Arch. internat. de pharmacodyn. et de therap.*, 1901, viii, 199-202.
25. TRUETA, J., et al.: Studies of the renal circulation, 1947, Blackwell, Oxford, Pp. 187.
26. MELLGREN, J., and REDELL, G.: Zur Pathologie und Klinik der Papillitis necroticans renalis, *Acta chir. Scandinav.*, 1941, lxxxiv, 439-457.
27. BOYD, E. M.: Lipopenia of fever, *Canad. Med. Assoc. Jr.*, 1935, xxxii, 500-506.

the portal venous system, since this type of vascular pathology has been found both in the intra- and extrahepatic groups.

The normal venous pressure in the portal system is higher than in the systemic veins because the portal blood after passing through the capillaries of the gastrointestinal tract, spleen and pancreas must traverse another capillary bed, the liver sinusoids, before it enters the inferior vena cava. The normal portal venous pressure has been found to be 10 to 15 cm. of saline. In the presence of portal bed block, either intra- or extrahepatic, the state of so-called portal hypertension develops with pressures varying from 25 to 50 cm. of saline. One of the collateral channels whereby the portal blood returns to the systemic venous system in these conditions is the esophageal veins. These vessels do not anastomose freely with the systemic system so that they frequently become greatly enlarged and varicosed. Hemorrhage from them is a common complication of portal hypertension and carries with it a very high mortality rate. The cause of rupture of these blood vessels has not been satisfactorily explained, but in part it is believed due to the relatively high venous pressure within them. Wangenstein<sup>2</sup> has suggested that it may be due to peptic ulceration of the esophageal mucosa over them, because of the reflux of acid gastric contents into the esophagus.

### DIAGNOSIS

The diagnosis of bleeding esophageal varices should be considered along with the other causes of esophageal-gastrointestinal bleeding in any patient who gives a history of hematemesis or melena. A sudden massive hematemesis is frequently the first sign that a patient has a portal bed block, especially of the extrahepatic type, since there are few premonitory symptoms of the disease. The diagnosis of a portal bed block with esophageal varices is suggested by such a history, especially if an enlarged spleen is found on physical examination. The blood, as a rule, shows a secondary anemia, a leukopenia and a thrombocytopenia. If the block is intrahepatic the liver may be shrunken, normal or enlarged and in the extrahepatic it is usually normal in size. The two types may be further differentiated by liver function tests. When the block is intrahepatic, there is usually a high retention of bromsulfalein, a reversal of the albumin-globulin ratio with a low level of serum albumin, a positive cephalin flocculation test and an elevated prothrombin time. If the block is extrahepatic all these liver function tests are usually normal. The most important diagnostic procedure, however, in patients suspected of having bleeding esophageal varices is a roentgenologic examination of the esophagus with a thick suspension of barium, as first described by Wolf<sup>3</sup> and later Schatzki<sup>4</sup> (figure 1). The visualization of the blood vessels by this technic depends to a great extent on the skill of the roentgenologist. Direct visualization of the lower end of the esophagus by esophagoscopy is another aid in diagnosis. The demonstration of esophageal



General Hospital over a 12 year period from 1934 to 1945. He found that in the cirrhotic group only 40, or 37 per cent, were alive one year after the diagnosis of esophageal varices was made. In the Banti's syndrome group 18, or 90 per cent, were alive. This higher mortality rate in the patients with cirrhosis is due undoubtedly to the fact that the patients are in an older age group. In addition and of extreme importance is the fact that they for the most part have severely damaged livers, whereas the Banti's group are relatively young and have essentially normal livers. Shull<sup>8</sup> in these same patients found that in the cirrhotic group 90, or 83 per cent, died from all causes. Of extreme significance, however, he found that 41, or 45 per cent, of those that died succumbed to massive esophago-gastrointestinal hemorrhage. In the Banti's group, seven, or 35 per cent, died from all causes and of these five, or 71 per cent of the deaths were due to hemorrhage. The mortality rates from hemorrhage alone in all the patients of the two groups were 38 per cent for the cirrhotics and 25 per cent for the Banti's syndrome group. In addition it is believed that hemorrhage was an important contributing factor in the death of many of the other patients who died from liver failure and other causes. This is especially apt to be true in a group with intrahepatic block, because in many of these patients the serum albumin level is already low due to the liver disease, and as a result of the severe hemorrhage a further rapid reduction takes place. Moreover in the presence of a diseased liver restoration of the serum albumin to a normal level seldom occurs.

The analysis of these cases is of great significance, since it demonstrates the grave prognosis once esophageal varices are diagnosed and the high mortality rate due to hemorrhage from them. At best bleeding esophageal varices cause prolonged disability, since patients after severe hemorrhage frequently require many weeks to months of hospitalization with expensive therapeutic measures. Numerous blood transfusions are essential in many cases to prevent death from shock, and in some cases the blood escapes almost as fast or faster than it can be administered. Under such conditions the bleeding may only be stopped by the placing of a balloon in the stomach which, after inflation, is drawn up against the cardia by means of traction on the rubber tube to which the balloon is attached, as reported by Rowntree et al.<sup>9</sup>

✓ The realization of this high morbidity and mortality due to the bleeding from esophageal varices has spurred us on in an attempt to lower the portal hypertension and reduce the amount of blood in the esophageal varices by formation of various types of portal systemic venous shunts. The treatment of bleeding esophageal varices by various surgical procedures has been attempted for many years. The demonstration by Eck<sup>10</sup> in 1877 that the portal venous blood could be shunted directly into the systemic venous system by anastomosing the portal vein directly to the inferior vena cava in experimental animals, thereby by-passing the liver, stimulated surgeons in the latter part of the 19th century and the early part of the 20th century to perform

tube method, thereby reducing the incidence of thrombosis at the site of the anastomosis. Sixth, there are no vital structures in the left upper quadrant of the abdomen, the region through which the surgical approach is made for this type of shunt, similar to the common bile duct or the hepatic artery which lie in such close proximity to the region where it is necessary to dissect out the portal vein and the inferior vena cava to perform a direct portacaval anastomosis. This last is a point of great practical importance since in either type of shunt operation structures are obscured frequently by bleeding from innumerable small collateral venous channels. An error of a few millimeters in the region of the gastrohepatic ligament in searching for the portal vein may irreparably damage the common bile duct or the hepatic artery with serious consequences, whereas in the splenic area such catastrophes are not as likely to occur since the margin of safety in this region can be measured in centimeters rather than millimeters.

During the past four years at the Massachusetts General Hospital from 1945 to 1948 inclusive, 34 patients with portal hypertension have had various types of portal systemic venous shunts constructed by the suture technic for bleeding esophageal varices. These operative procedures have not been performed on patients unless there was a history of esophago-gastrointestinal bleeding, nor have they been done for the relief of ascites alone. It has been considered advisable in developing this new type of surgery to subject only those patients in whom severe or repeated hemorrhages have taken place in an attempt to see whether future bleedings could be prevented. In this group of patients there were 20 with the intrahepatic type of portal bed block due to cirrhosis of the liver and 14 patients with Banti's syndrome, or congestive splenomegaly, the extrahepatic type of portal bed block. The youngest patient in the group was six years of age and the oldest 65 years. Both had the extrahepatic type of portal bed block, the former presumably of congenital origin due to obliteration of the portal vein and the latter due to thrombosis of the portal venous system of idiopathic origin. The mean age in this group was 36 years. The ages of the intrahepatic group due to cirrhosis of the liver ranged from 27 years to 60 years with a mean age of 44 years. Seven patients in the latter group died as a result of the operative procedure, a mortality rate of 35 per cent. There were no deaths in the Banti's syndrome group, making an operative mortality rate of 21 per cent for the entire group. It is of interest that the operative mortality rate has dropped with the increased experience gained in this type of surgery and the better selection of patients for the procedure, since 20 patients were operated upon in the year 1948 with two deaths, an operative mortality rate of only 10 per cent. Both of them occurred in the cirrhotic group. These statistics indicate, as might be expected, that the risk of this type of surgery which frequently requires four to six hours of anesthesia is greater in those patients with cirrhosis because of the underlying liver disease.

An analysis of the causes of death in these seven patients reveals that four of them died within a few hours of uncontrollable hemorrhage from the

pexy; second, ligation of the coronary vein of the stomach and a second omentopexy; and third, a transthoracic ligation of the peri-esophageal veins.

A direct portacaval shunt, the Eck type of fistula, anastomosing the portal vein to the inferior vena cava was attempted in eight patients. It was possible to perform it in only three of them because in the other five the extreme vascularity in the region of the gastrohepatic ligament prevented exposure of the portal vein. In one patient the common bile duct and gall bladder were injured, necessitating a choledochojejunostomy to reestablish the flow of bile into the intestinal tract and also a cholecystectomy. This patient at a later operation had a splenectomy and a satisfactory end-to-side splenorenal shunt performed. The direct portacaval type of anastomosis was chosen in these eight patients for various reasons. Splenectomy had been previously performed in five of them, which has been found to preclude the construction of a splenorenal shunt at a later date because of thrombosis and secondary fibrosis of the splenic vein. For this reason it was necessary to attempt some other form of shunt in these patients and the direct portal vein to inferior vena cava type of anastomosis was chosen. In two other patients this procedure was selected because the spleen in both was only slightly enlarged, indicating that the splenic vein would not be large enough with which to create a shunt of sufficient size to reduce the portal hypertension. In the remaining patient it was chosen because three other surgeons who had operated upon him had considered a splenectomy to be too formidable a procedure to perform, so that a direct portacaval shunt was attempted almost of necessity. It is of interest that the portal bed block was intrahepatic in three of the patients and extrahepatic in the other five. Two of the patients died; one in whom the shunt was constructed succumbed because of thrombosis of the hepatic artery, the result of operative trauma. In the other one the operation had to be discontinued even before the portal vein was exposed because of uncontrollable bleeding in the operative field and despite numerous transfusions the patient died from postoperative hemorrhage. Both of these patients had the intrahepatic type of portal bed block with severe impairment of liver function from portal cirrhosis, which undoubtedly played some rôle in their deaths.

A successful portacaval anastomosis with survival was performed in only two of the patients, one with intrahepatic block and the other of the extrahepatic type. Both of these patients had had previous splenectomies without relief from massive bleeding. It is at least encouraging that they are alive and have had no further esophago-gastrointestinal hemorrhages for periods of six months in one case and 12 months in the other. The difficulty encountered in attempting to perform a portal vein to inferior vena cava shunt in patients with the so-called Banti's syndrome, the extrahepatic type of portal bed block, who have had previous splenectomies cannot be over-emphasized, as has already been reported,<sup>15</sup> since in four of these previously splenectomized patients it was possible only in one to create a satisfactory shunt.

improved since the postshunt episodes of hemorrhage have not been as severe as the prior ones.

In summary, it can be stated that the construction of various types of portal systemic venous shunts represents a new chapter in the treatment of bleeding esophageal varices, a condition which heretofore has failed to respond to other forms of treatment. In the four year period from 1945 to 1948 inclusive, 34 patients at the Massachusetts General Hospital have been subjected to this type of surgery because of the chief complaint of massive esophago-gastrointestinal hemorrhages. The chief benefit from this type of procedure, that has been observed to date, has been the cessation of bleeding in a majority of patients that have had a satisfactory shunt performed, either a direct portacaval or a splenorenal type. There are 24 patients in this group that can be classified in this category and only one of them has bled since the operation was performed, an incidence of only 4 per cent of bleeding.

The postoperative follow-up studies in reference to liver function at present are incomplete. The bromsulfalein retention test and the serum albumin level in the cirrhotic group of patients reveals little if any improvement in these functions of the liver. In the Banti's syndrome group, they reveal little if any impairment following the construction of the shunt. The cephalin flocculation test in the majority of the cirrhotic patients shows slight improvement from  $4+3+$  to  $3+-2+$ . The most striking improvement has been in the level of the hemoglobin, as would be expected, since esophago-gastrointestinal bleeding has ceased in the majority of patients. The pre-operative levels varied from 7.4 to 12.4 grams of hemoglobin per 100 cubic centimeters of blood and the postoperative levels have been maintained at from 11 to 17.5 grams of hemoglobin. The period of postoperative follow-up is of necessity short, but it ranges from four to 34 months. A true evaluation of the procedure necessarily must await a greater lapse of time, but at the present writing the results are definitely encouraging.

### CONCLUSIONS

1. The establishment of portal systemic venous shunts represents a new and encouraging chapter in the treatment of bleeding esophageal varices secondary to portal hypertension.
2. Splenectomy and the suture type of end-to-side splenorenal anastomosis with preservation of the kidney is recommended as the most satisfactory operative procedure.
3. It is believed that a surgeon should not do a splenectomy in a case of portal hypertension unless he is prepared to do a splenorenal anastomosis at the same operation, since this may be the only opportunity to construct a satisfactory portal systemic venous shunt.
4. The postoperative studies over periods of 4 to 34 months in patients in whom satisfactory portal systemic venous shunts have been performed

# PHARMACODYNAMICS OF PULMONARY ABSORPTION IN MAN. II. THE INFLUENCE OF VARIOUS DILUENTS ON AEROSOL AND INTRATRACHEAL PENICILLIN\*

By JOHN F. BEAKEY, EDWARD A. GAENSLER and MAURICE S. SEGAL, F.A.C.P., *Boston, Massachusetts*

THE pharmacodynamics of pulmonary absorption has not been generally considered in the clinical reports on the success of aerosol and intratracheal therapy. There is equally meager information regarding the action of various pharmacologically active diluents in promoting or retarding absorption of penicillin from the pulmonary epithelium.

In a recent study<sup>1</sup> we described various factors influencing absorption from the normal human lung. Crystalline penicillin G potassium (100,000 units) in physiologic saline was administered intramuscularly, intratracheally and by oxygen-aerosolization. The blood levels and urinary excretion, following intratracheal injection, were lower but more sustained than those following intramuscular administration. Rapid absorption would normally be expected from such a large and vascular area as the alveolar bed. The lung was thus demonstrated as a reservoir capable of considerably retarding the expected rate of absorption. By comparing the total urinary excretion of the intratracheal with aerosol method of administration, the amount of penicillin actually reaching the lung by the latter route was calculated to be about 35 per cent. Easily determinable wastage, occurring during aerosolization, accounted for some of the loss.

Although physiologic saline has been most generally used as the diluent or vehicle for penicillin aerosolization, other diluents, which are active substances themselves, have been suggested. Inhalation of 0.5 to 1 per cent adrenalin has been notably effective in relieving bronchospasm in the asthmatic;<sup>2,3</sup> neosynephrin is a potent bronchovasoconstrictor which shrinks mucous membranes rapidly. Combination of either or both of these two solutions with penicillin was a natural development when the need arose for such medication in addition to penicillin itself. While such vehicles have been used with penicillin, others suggest themselves as effective diluents because of their inherent pharmacological activity. The search for diluents which might either enhance or supplement the action of penicillin or act independently to advantage has attracted relatively few investigators.

\* Received for publication September 11, 1948.

From the Department of Inhalational Therapy, Boston City Hospital and the Department of Medicine, Tufts College Medical School.

This study was aided by a grant from the Commercial Solvents Corporation.

tion occurring with their use must be attributed to a local chemical or mechanical action.

### RESULTS

For an analysis of data in terms of therapeutic effectiveness, the bactericidal activity *in vitro* must be correlated *with* clinical or *in vivo* results. The average minimal effective level at which most gram-positive pathogens are killed faster than they multiply, or the concentrations at which these organisms fail to grow in culture, is 0.04 (0.039) unit of penicillin per c.c. of serum. For purposes of analysis, therefore, we elected to call this the "minimum therapeutic level." This, and higher levels, we have called "positive"; levels less than 0.04 unit per c.c. of serum we have called "negative."

Following aerosolization of penicillin in each diluent, serum levels were evaluated according to the above criteria. The overall effectiveness of a diluent was judged by the following determinations. First, by the number of sera at or exceeding 0.04 unit per c.c. throughout the entire two hours;

CHART I

Diluent	Physiologic Saline	Neosynephrin (1%)	Epinephrine (1%)	Triethylene Glycol (100%)	Chlorophyll (100%)	Pantopaque (100%)
No. of sera tested	36	35	33	33	27	26
Total percentage of positive sera*	69	66	33	18	44	11
Percentage of sera still positive at the end of two hours	25	45	9	9	0	11
Percentage of sera exceeding minimum therapeutic level	39	29	9	9	22	0

\* 0.04 unit or more.

this is expressed as the *total percentage of positive sera* for each vehicle. Second, by the ability of any particular diluent to affect absorption so that blood levels are positive for a longer period of time; this is reflected in the *percentage of sera still positive at the end of two hours*. Third, by the *percentage of sera whose penicillin activity exceeds the minimum therapeutic level* (i.e. more than 0.04 unit per c.c. of serum). Determination of the latter is important since the "minimum therapeutic level" is insufficient for complete bactericidal activity against many strains of susceptible organisms. Diluents which will so affect absorption that levels in a higher range result, must, therefore, be considered particularly effective. A summary of each aerosolized diluent analyzed according to these criteria is given in chart 1. Neosynephrin is a potent bronchovasoconstrictor with poor bronchodilator properties; epinephrine has less vasoconstrictor properties but is a

powerful bronchodilator. One per cent neosynephrin and 2.5 per cent racemic epinephrine (Vaponefrin, analogous to 1.5 per cent U.S.P. epinephrine) were used as diluents. The effects on absorption of these two drugs as contrasted to saline were reflected in the blood levels (chart 2 and figure 1).

The total percentage of positive sera with saline (69 per cent) and neosynephrin (66 per cent) are essentially the same; whereas, only 33 per cent

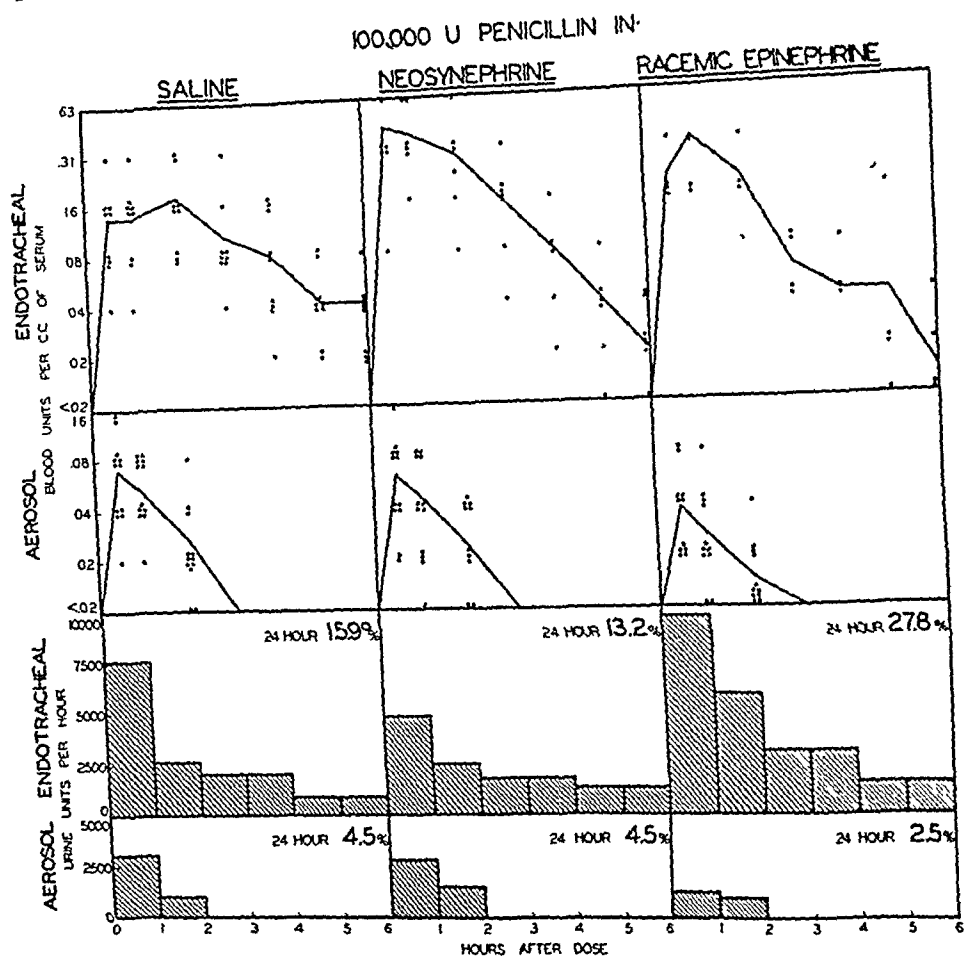


FIG. 1. Blood level curves and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by intratracheal and aerosol routes of administration in various diluents.

positive sera were obtained with racemic epinephrine (chart 1). The differences in the percentage of sera still positive at the end of two hours demonstrate the vasoconstricting action of neosynephrin on the absorption of penicillin; 45 per cent of the two-hour sera were positive as compared to 25 per cent with saline and only 9 per cent with epinephrine. The percentage of sera exceeding the minimum therapeutic level follows much the same pattern: with saline, 39 per cent, with neosynephrin, 29 per cent; and with epinephrine, 9 per cent. Total urinary excretions were consistent with the blood

priate for intrapulmonary use. Since triethylene glycol and Pantopaque are relatively viscid and not easily aerosolized by the conventional nebulizer, a special Vaponefrin nebulizer, dispensing a larger particle size, was used.

These diluents, whose effect on absorption and excretion of penicillin is of a chemical or mechanical action, have a marked effect on the serum levels (chart 2 and figure 2). The blood levels and total urinary excretion were consistently lower than those obtained with physiologic saline. The *total percentage of positive sera* (chart 1) using triethylene glycol (18 per cent) or Pantopaque (11 per cent) compare unfavorably with that of saline (69 per cent); chlorophyll produced a somewhat higher number of sera in the therapeutic range (44 per cent). The *percentage of sera positive at the end of two hours* and the *percentage of sera whose penicillin activity exceeded the minimum therapeutic level* also did not compare favorably to that of saline when these diluents were used.

### INTRATRACHEAL ADMINISTRATION

Direct instillation into the trachea should yield accurate data on the manner in which diluents affect absorption of penicillin from the tracheo-bronchial tree. With aerosolization, losses occur at the apparatus, into the air and in the mouth. We have shown elsewhere that only 35 per cent of an aerosolized substance actually reaches the lung. Exact quantitative evaluation is therefore difficult. In contrast, no losses occur with intratracheal administration unless the injected substance causes enough chemical irritation to produce cough and expectoration in spite of topical anesthesia.

We, therefore, elected to inject directly into the trachea the same diluents previously used by the aerosol route. Penicillin assay of bloods and urines following this type of administration were tabulated (chart 3) and correlated with the aerosol data (figures 1 and 2).

The results following the use of neosynephrin, epinephrine and saline as penicillin vehicles, by both aerosol and intratracheal routes, are compared in figure 1. Neosynephrin 1:100 was used for aerosolization but was diluted to 1:1,000 for intratracheal injection; racemic epinephrine (analogous to 1.5 per cent U.S.P. epinephrine) was employed for inhalation; and epinephrine for direct instillation was diluted to a 1:10,000 concentration because marked side reactions occurred with higher concentrations. Despite such low dilutions, these substances exerted a profound effect on the blood levels and urinary excretion of penicillin when injected endotracheally.

Certain striking facts are partially obscured by the logarithmic ordinates of our graphs. Actually, the average blood level at one-half hour following neosynephrin (0.43 unit) was exactly three times that obtained when saline was the diluent (0.14 unit). The ratio was maintained fairly closely at one hour and less so at two hours; at four hours, the average levels were the same (0.08 unit). The neosynephrin curve remained within the therapeutic range for five hours; the saline curve remained so for six hours. The



CHART III—Continued

	Blood							Urinary Excretion					
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.	Total
Pantopaque													
P. M.	.63	.31	.08	.16	.08	.04	.02	33,250	8,500	17,500	15,375	89	74,714
P. F.	.31	.31	.08	.04	.03	.02	.01	27,000	10,500	16,500	402	200	54,602
A. H.	.16	.08	.04	.02	—	0	0	—	—	—	—	—	—
J. F.	.31	.16	.08	.04	.02	0	0	33,750	5,000	8,375	2,122	162	49,409
J. O'D.	.31	.31	.08	.08	.03	0	0	12,500	4,992	6,718	800	200	25,210
Average	.34	.23	.07	.07	.04	.01	.01	26,625	7,248	12,273	4,675	162	50,983
Human Serum													
J. C.	.23	.08	.08	.04	.02	0	0	4,000	4,000	2,500	2,500	115	12,115
R. C.	.16	.16	.16	.08	.02	.02	0	6,240	6,240	12,500	12,500	438	37,918
R. W.	.16	.08	.08	.06	.06	.04	.04	12,500	12,500	12,500	6,240	1,575	45,315
J. H.	.31	.63	.31	.31	.16	.08	.04	18,740	25,000	12,500	1,560	2,850	60,650
Average	.22	.24	.16	.12	.07	.04	.02	10,370	11,935	10,000	5,700	1,245	39,250

penicillin blood curve with endotracheal epinephrine lay between the neosynephrin and saline curves and remained within the therapeutic range for five hours.

The amount of penicillin excreted in the urine following endotracheal administration with these diluents varied. Average recovery in the urine after the use of epinephrine was greater at each time interval than with either neosynephrin or saline and the total average excretion was approximately twice that obtained with either of the other vehicles. Although the total average excretion with neosynephrin was slightly lower than with saline, most of this difference occurred in the first hour; after the fourth hour, recovery with neosynephrine was moderately higher than with saline.

The blood level curves following aerosolization of penicillin in each of these diluents have been fully discussed above. Correlation with the endotracheal data just presented discloses fair consistency. However, the lower recovery in the urine following aerosolization with epinephrine is inconsistent with the comparatively high recovery following intratracheal injection with this same substance.

The absorption and excretion of penicillin when injected endotracheally with triethylene glycol, chlorophyll or Pantopaque is compared to saline (figure 2). A micronized crystalline penicillin G potassium powder with an average particle size of less than two micra was mixed with Pantopaque when this substance was studied intratracheally. Unlike all other substances which we injected into the trachea, chlorophyll and especially triethylene glycol were markedly irritating in 100 per cent concentrations and varying amounts of penicillin were lost because of resultant cough and expectoration. It is noteworthy that instillation of Pantopaque did not lead to cough.

bination with penicillin when the clinical picture warranted the use of either to combat bronchospasm, mucosal swelling or both. On the contrary, definite beneficial local effects, in addition to their pharmacologic actions, appeared to be exerted.

Triethylene glycol did not seem to hold any particular advantage as a diluent by either the aerosol or intratracheal routes. As it was too viscid for easy aerosolization with the conventional nebulizer, the blood levels following its administration with a special large particle size nebulizer were disappointing. Moreover, by intratracheal route, it was extremely irritating to the tracheobronchial tree. Low blood levels and urinary excretion may be argued as indicating local retention in the lung; in fact, studies in which triethylene glycol was tagged with radioactive substances indicated a greater local retention of penicillin when combined with this diluent than with other substances.<sup>17</sup> A slowing of absorption would, of course, result in low early blood levels but, conversely, blood samples at later intervals would continue to show penicillin activity, albeit still in the lower ranges. Following intratracheal injection, all individual six-hour levels and one-half of the five-hour levels were zero. Following aerosolization, only one of the 11 sera tested at the end of two hours was within a therapeutic range. With neither route, therefore, could delayed absorption be ascribed to a glycol-penicillin combination. Other reports have described the glycols as enhancing the bactericidal action of penicillin when combined with the latter. In fact, a bactericidal action of glycol alone in the blood stream has been claimed.<sup>18</sup> However, these conclusions were based on a bacteriological technic which used *B. subtilis* as a test organism; normal blood has been shown to exhibit antibodies in various titers for these organisms.<sup>19</sup> A false impression of bactericidal activity in the serum may, therefore, result when *B. subtilis* is used as the test organism. In addition to our routine studies, we repeated the above mentioned study<sup>18</sup> where 100,000 units of penicillin was aerosolized in a mixture of 19 c.c. of triethylene glycol and 1 c.c. of glycerol. We employed the O.E.M. head-tent. A double assay of several blood and urine specimens was done using both streptococcus No. 98 and *B. subtilis* as test organisms. As we could not demonstrate any penicillin in either the blood or urine, we were, therefore, unable to detect either delay in absorption or potentiation of the bactericidal action of penicillin when it was combined with glycol.

Initial blood levels, with chlorophyll as a diluent, were higher than the saline levels, especially when administered intratracheally. With both routes, however, levels were not maintained within a therapeutic range for as long a time as with saline. Chlorophyll, in 25 per cent dilution, was not irritating to the tracheobronchial tree but full strength solution, when given intratracheally, did cause cough despite topical anesthesia. However, chlorophyll may be of practical value when the bacterial flora includes anaerobic organisms. Because it causes more rapid absorption of penicillin, its administration would have to be repeated at shorter time intervals.

2. Both neosynephrin and epinephrine, constrictors of the bronchial mucous membrane, caused higher initial blood levels than corresponding results with saline when injected intratracheally. Levels were sustained within a therapeutic range for five hours. The bronchovasoconstricting action of neosynephrin was more in evidence when aerosolized with penicillin.

3. When the aerosolization of either or both of these substances with penicillin was indicated clinically, their local pharmacologic action on the tracheobronchial tree favorably affected absorption of penicillin. Irritation or side reactions were not present with either route of administration.

4. Triethylene glycol was too viscid for easy aerosolization and too irritating, at full strength, for intratracheal injection. Neither a bactericidal action of its own, enhancement of penicillin activity in the serum nor a delaying action on the absorption of penicillin could be demonstrated.

5. Chlorophyll caused more rapid absorption of penicillin but levels were not maintained within a therapeutic range for as great a length of time as with saline. One hundred per cent solution was irritating to the tracheobronchial tree, but a 25 per cent solution was well tolerated by intratracheal instillation. Chlorophyll with penicillin, in the treatment of mixed gram positive and negative bacterial flora, should be repeated frequently in order to maintain high local antibiotic activity. Chlorophyll (endotracheal) should be of definite value for the management of anaerobic bacterial bronchopulmonary infections.

6. Intratracheal injection of emulsions of penicillin in the lighter iodized oils in the treatment of bronchopulmonary suppurative disease is discussed. The cleansing action of the oil at the site of localized collections of pus and the displacement or "floating" of mucous plugs would permit more effective local action of penicillin injected at the same time.

7. Human serum as a vehicle did not greatly alter the absorption of penicillin from the lung.

#### BIBLIOGRAPHY

1. GAENSLER, E. A., BEAKEY, J. F., and SEGAL, M. S.: Pharmacodynamics of pulmonary absorption in man. I. Aerosol and intratracheal penicillin, *Ann. Int. Med.*, 1949, xxxi, 582.
2. GRAESER, J. B., and ROWE, A. H.: Inhalation of epinephrine for the relief of asthmatic symptoms, *Jr. Allergy*, 1935, vi, 415.
3. SEGAL, M. S., and BEAKEY, J. F.: The use of 1-(3'-4'-dihydroxyphenyl)-2-isopropylamino-ethanol for the management of bronchial asthma. A preliminary report, *Bull. New England Med. Center*, 1947, ix, 62.
4. RAMMELKAMP, C. H.: A method of determining the concentration of penicillin in body fluids and exudates, *Proc. Soc. Exper. Biol. and Med.*, 1942, li, 95.
5. MEAKINS, J. C., SMITH, F., and GOLD, M. A.: A comparative study of some commercial preparations of oral penicillin, *Canad. Med. Assoc. Jr.*, 1946, lv, 97.
6. GOODMAN, L., and GILMAN, A.: *The pharmacological basis of therapeutics*, 1941, pg. 405, Macmillan Co., New York.
7. HARRIS, T. N., and STOKES, J., JR.: Summary of a three year study of the clinical application of the disinfection of air by glycol vapors, *Am. Jr. Med. Sci.*, 1945, ccix, 152.

# TREATMENT OF HEART AND KIDNEY DISEASE AND OF HYPERTENSIVE AND ARTERIO- SCLEROTIC VASCULAR DISEASE WITH THE RICE DIET \*

By WALTER KEMPNER, M.D., *Durham, N. C.*†

THE treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet is either ineffective or dangerous, unless it is done under rigidly controlled conditions. Ineffective, because small or "minimal" additions to the diet may spoil the entire therapeutic result; dangerous, because a strict observance of the diet may lead to a deficiency of vitally important elements unless care is taken that the equilibrium between intake and loss of these substances is maintained. For both reasons, therefore, continuous supervision, over a long period of time, including constant checks of blood and urine chemistry, is essential.

Rigidly controlled conditions are likewise indispensable for the evaluation of the therapeutic results. Claims of positive or negative results based on nothing but blood pressure readings for four to eight weeks before and after treatment and not substantiated by heart films, electrocardiograms, eye-ground photographs and chemical findings do not contribute much to the solution of this problem.

The same authors who a few years ago insisted that the restriction of salt, protein or fat is unwarranted in the treatment of hypertensive and arteriosclerotic vascular disease, now admit the importance of these dietary restrictions. No matter what the value of the restriction of sodium or of chloride or of protein or of cholesterol may be, the fact is: The rice diet contains less sodium and less chloride than any other diet which has been devised to reduce the sodium and chloride intake. It contains less protein than any other diet which has been devised to reduce the protein intake. It contains less cholesterol and other fat than any other diet which has been devised to reduce the cholesterol and fat intake.

The rice diet contains in 2,000 calories less than 5 gm. of fat and about 20 gm. of protein derived from rice and fruit and less than 200 mg. of chloride and 150 mg. of sodium. This does not mean that the patient's caloric intake is restricted to 2,000 calories; it varies according to whether weight gain or weight loss, protein increase or protein decrease is desirable in the individual patient.

\*Read at the Thirtieth Annual Session, American College of Physicians, New York, N. Y., March 30, 1949.

From the Department of Medicine, Duke University School of Medicine.

† This work was supported by grants from the A. H. Hanes Research Fund, the Life Insurance Medical Research Fund, and the U. S. Public Health Service.

and urine shows that the nitrogen equilibrium on the rice diet can easily be maintained (table 1).

There are other indications that, because of the protein sparing action of the carbohydrates, the protein part of the rice diet is adequate and that there is no lack of essential amino acids; e.g., the fact that the production of hemoglobin is normal and that anemia does not develop. Also the fact that blood urea and non-protein nitrogen decrease on the rice diet whereas in starvation and in protein deficiency the body uses its own protein and the non-protein nitrogen and the urea nitrogen in the blood increase.

Other differences between starvation and the rice diet are: in starvation, the serum calcium is decreased, on the rice diet unchanged. In starvation, the plasma protein and the A/G ratio are decreased, on the rice diet unchanged or, if low before, often become normal. In starvation, the blood sugar is decreased, on the rice diet unchanged. In starvation, the carbohydrate tolerance is decreased, on the rice diet increased. In starvation, the serum phospholipids are increased, on the rice diet decreased. In starvation, the CO<sub>2</sub> combining power is decreased, on the rice diet increased. In star-

TABLE I  
Nitrogen Balance After 60 Days on Rice Diet, gm.N in 24 hrs.  
(Averages of 4 consecutive days)

	Intake	Output		Balance
		urine	stool	
W. C. m., 59	4.66	2.61	1.81	+0.24
		4.42		

vation, the blood volume remains unchanged or—in relation to body weight—increases; on the rice diet, according to Murphy's determinations, it decreases. In starvation, the interstitial fluid remains unchanged or increases; on the rice diet it decreases. (N. B., there is no simple relationship between volume changes and clinical course.) In starvation, the excretion of total creatine bodies in the urine is unchanged; on the rice diet it is decreased. In starvation, the excretion of creatine, ammonia and organic acids is increased, on the rice diet decreased. In starvation, the excretion of total sulfate and inorganic phosphate is decreased, on the rice diet markedly decreased (table 2).

In 490 patients with hypertensive vascular disease and an initial non-protein nitrogen of 20 to 45 mg. per 100 c.c. of blood, there was an average decrease of the non-protein nitrogen from 33 to 28 mg. per 100 c.c. of blood after an average period of 98 days. There was an average decrease of the urea nitrogen from 14 to 8 mg. (table 3). These figures are also interesting in another connection: a decreased salt intake in the diet with ensuing hypochloremia is usually followed by an increase in the blood urea nitrogen.

various proteins. It is of no advantage to the patient to receive a large amount of protein with a low biological value which cannot be properly utilized. Moreover, certain patients should use protein only for essential purposes and not merely to supply calories which can just as well be supplied by the oxidation and fermentation of carbohydrates.

The same considerations which apply to protein and essential amino acids are also valid with regard to fat and essential fatty acids. The absolute fat content of rice for instance is small, but the proportion of linoleic acid, an essential fatty acid, is high.

One of the lipids which is supposed to have an important rôle in the development of vascular disease is cholesterol. A high cholesterol concentration in the serum is frequently found in arteriosclerosis, coronary artery disease, exudative vascular retinopathy, hypertensive vascular disease, as well as in diseases of the lens and vitreous body, in uncontrolled diabetes mellitus and in the nephrotic stage of nephritis.

TABLE IV  
Total Serum Cholesterol of 511 Patients with Hypertensive Vascular Disease

	Before	After	Average Period of Rice Diet (Days)
	Rice Diet		
148 Patients with initial concentration below 220 mg. per 100 c.c. serum	186	171	120
363 Patients with initial concentration above 219 mg. per 100 c.c. serum	279	205	102

An easy way to produce arteriosclerosis is by feeding cholesterol to rabbits. In dogs it is not so easy. The aging process in the human species seems to be a change from the dog state to the rabbit state. The cholesterol metabolism becomes inadequate and the average serum cholesterol concentration of men of 50 is higher than that of men of 20 who have an identical cholesterol intake. However, if a 20 year old man has a disease which causes a hypercholesterolemia, the same sequelae may occur as in the 50 year old man. The literature describes cases of arteriosclerosis in diabetic children as young as one year.

We have examined the effect of the rice diet on the total serum cholesterol of 511 patients with hypertensive vascular disease (table 4). In 148 patients (29 per cent) who started the rice diet with a normal serum cholesterol, the average decrease was 15 mg. per 100 c.c. of serum after an average period of 120 days. In 363 patients (71 per cent) who had a hypercholesterolemia before the rice diet, the average decrease was 74 mg. after an average period of 102 days.

These figures show that, no matter from what fatty or non-fatty substances the cholesterol in the body is derived, and by what mechanism a high

TABLE VI

Lipid Phosphorus in Serum of 42 Patients with Hypertensive Vascular Disease  
(Mg. lipid P in 100 c.c. serum)

Before	After 78 Days (Average) on
Rice Diet	
9.91	8.87

ACIDS AND BASES IN URINE  
*NORMAL*

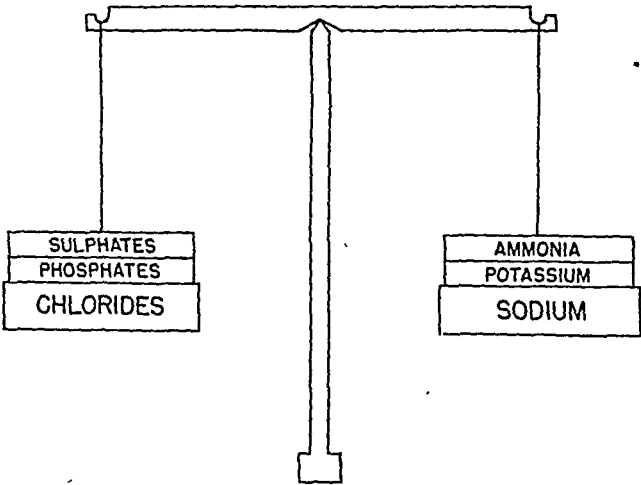


FIG. 3.

ACIDS AND BASES IN URINE  
*RENAL INSUFFICIENCY*

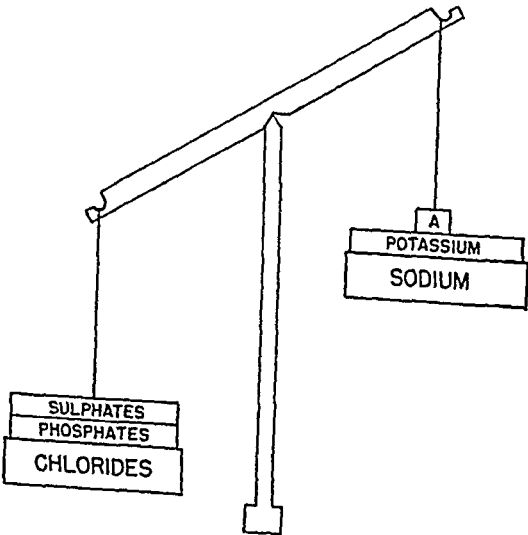


FIG. 4.

Now let me turn from the chemical changes to the clinical changes produced by the rice diet. I will avoid long-winded statistics as much as possible and will try to discuss the main problems by showing you some typical cases as examples of what can be achieved in the individual patient.

The first case is that of a 13 year old school girl in the nephrotic stage of chronic nephritis. It is an example of the disappearance of marked generalized *renal* edema and hypoproteinemia on the rice diet. Early in Jan-

B.H. (f. 13) Nephrotic Stage of Chronic Glomerulonephritis



6-18-48	160 lbs	10-7-48	97 lbs
10.1 Gm.	protein per 1000 cc urine	0.17 Gm.	
4.0 Gm	protein per 100 cc. serum	5.8 Gm	
540 mg	cholesterol per 100 cc serum	185 mg.	

FIG. 6.

uary, 1948, this girl developed swelling of the lower extremities after a sore throat. She was treated by bed rest, salt-poor diet (for part of the time, high protein diet), and penicillin. In February, 1948, massive anasarca developed; a paracentesis was done which resulted in a weight loss of 22 pounds. Later, because of marked dyspnea, a thoracocentesis was necessary and one quart of fluid was removed from the right pleural cavity. During June, the facial edema which had been present since January became worse and the general edema and ascites increased. When the oliguria became serious, the patient was referred to us. The rice diet was started on June 18, 1948. No further paracentesis or thoracocentesis was done. The albuminuria decreased from 10.1 gm. per liter (average during the first 20 days on the rice diet) to 0.17 gm. (average after 111 to 131 days of rice diet). The



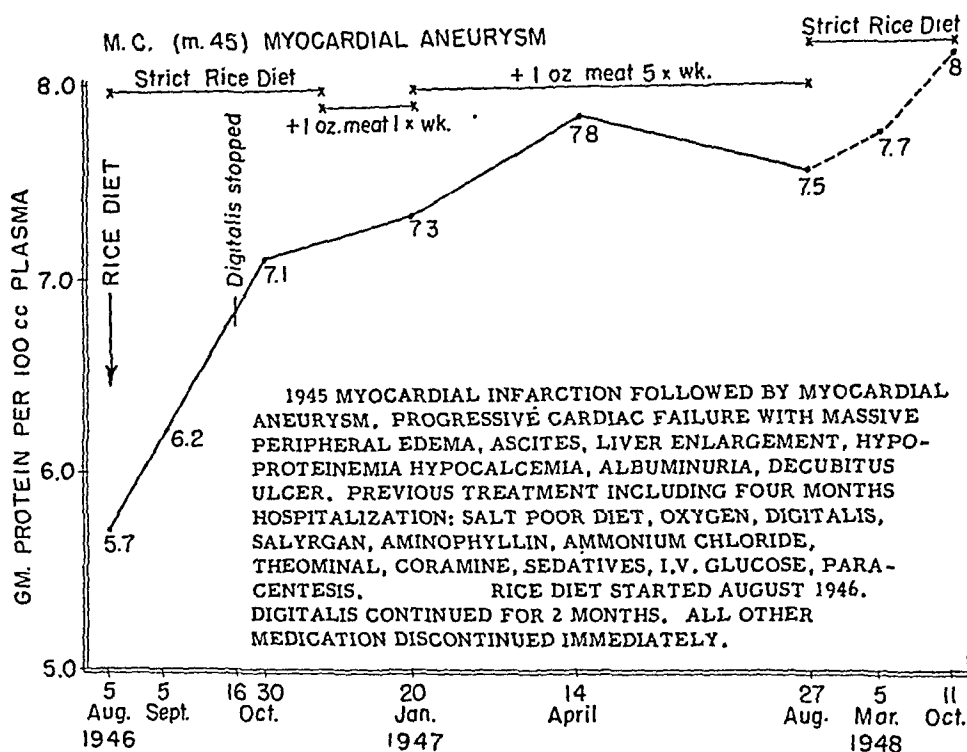


FIG. 8.

plasma protein increased from 4.0 gm. to 5.8 gm. The cholesterol decreased during this period from 540 mg. per 100 c.c. of serum to 185 mg. There was a total weight loss of 63 pounds in 15 weeks with gradual disappearance of ascites and pleural effusion. After eight months on the rice diet, the

M.C. (m.45)

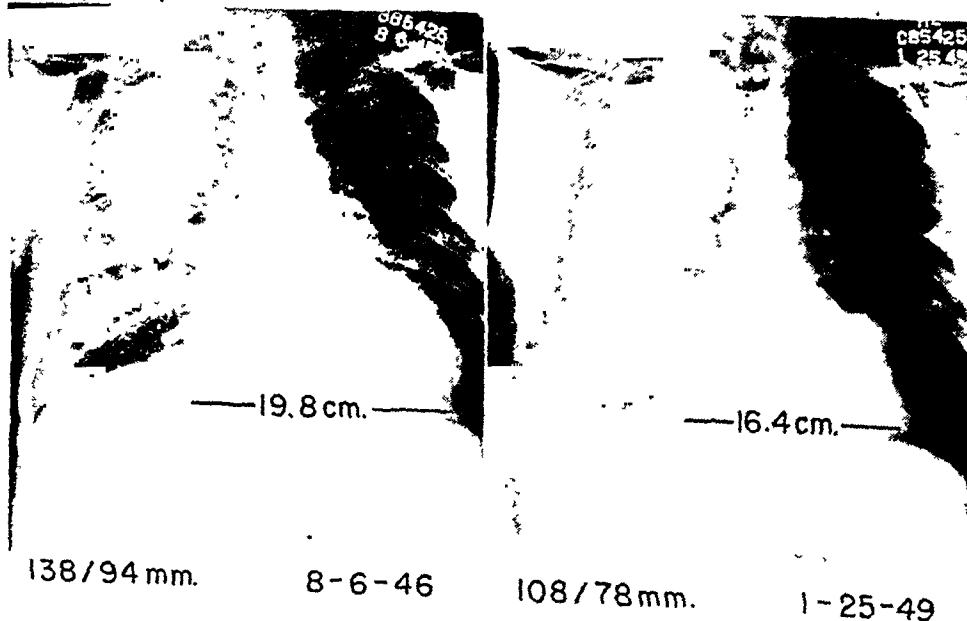


FIG. 9.

was followed by a myocardial aneurysm, progressive cardiac failure with massive peripheral edema, ascites, liver enlargement, hypoproteinemia, hypocalcemia, albuminuria, and decubitus ulcers. Previous treatment, including four months' hospitalization, consisted of salt-free diet, oxygen, digitalis, salyrgan, aminophyllin, ammonium chloride, theominal, coramine, sedatives; i.v. glucose; paracentesis. The rice diet was started August 7, 1946, and was strictly followed; a paracentesis was done August 13. Digitalis was continued for two months, but all other medications were discontinued immediately. There was a loss of weight (edema) of 50 pounds in 10 weeks. Up to the present time (two and one-half years later), the patient has received no medication; he is up and around and completely asymptomatic. The plasma proteins have increased from 5.7 gm. per 100 c.c. to 8.2 gm.

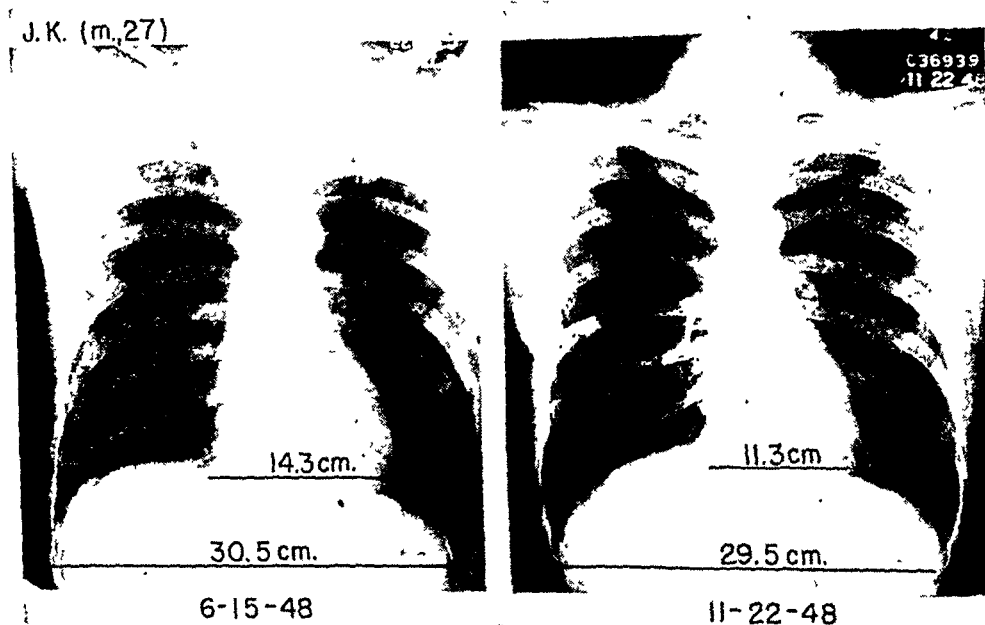


FIG. 11.

The heart is considerably smaller and the aneurysm of the posterior lateral wall of the left ventricle is now clearly visible in the A-P view (figure 9).

The patient, whose eyeground photographs and chest films are shown in figures 10 and 11, is an example of the effect of the rice diet on retinopathy and cardiac enlargement in chronic glomerulonephritis.

The patient was a 27 year old man who two years before admission to Duke Hospital, while in the Navy, had scarlet fever and acute glomerulonephritis, followed by chronic glomerulonephritis. He had been hospitalized for 16 months and treated with rest and various diets. During the month prior to admission, the patient had an exacerbation of his headache, noted blurring of vision and had a generalized convulsion, for which magnesium sulfate was given. At the start of the rice diet the blood pressure was 180

regained his eyesight; papilledema, hemorrhages and most of the exudates had disappeared; the heart had decreased in size with a change in the transverse diameter of 27 per cent.

I have shown you some effects of the rice diet on edema, ascites, heart enlargement and retinopathy in patients with primary kidney disease. I will show you now some characteristic examples of the effect of the rice diet on hypertensive vascular disease without evidence of any primary renal disease. In more than 70 per cent of 777 patients most of whom were seriously ill and had failed to respond to other forms of treatment, the rice diet, given for periods of four to 1,150 days (average 92 days), has proved beneficial; that means that it has produced one or more of the following effects: decrease in the sum of systolic and diastolic blood pressure of at least

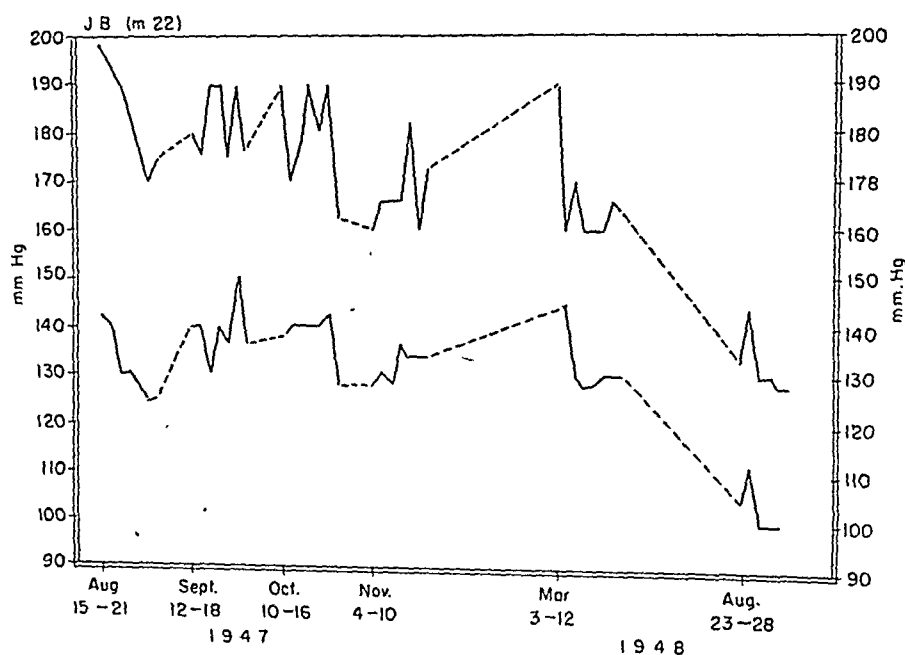
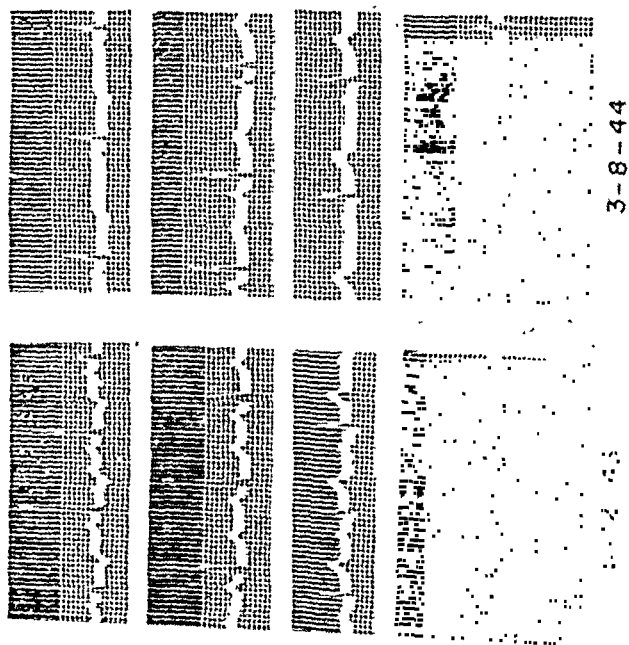
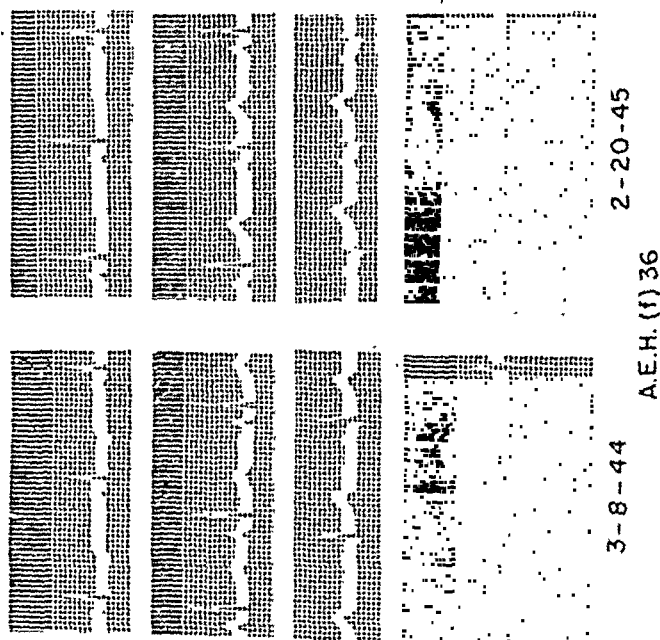
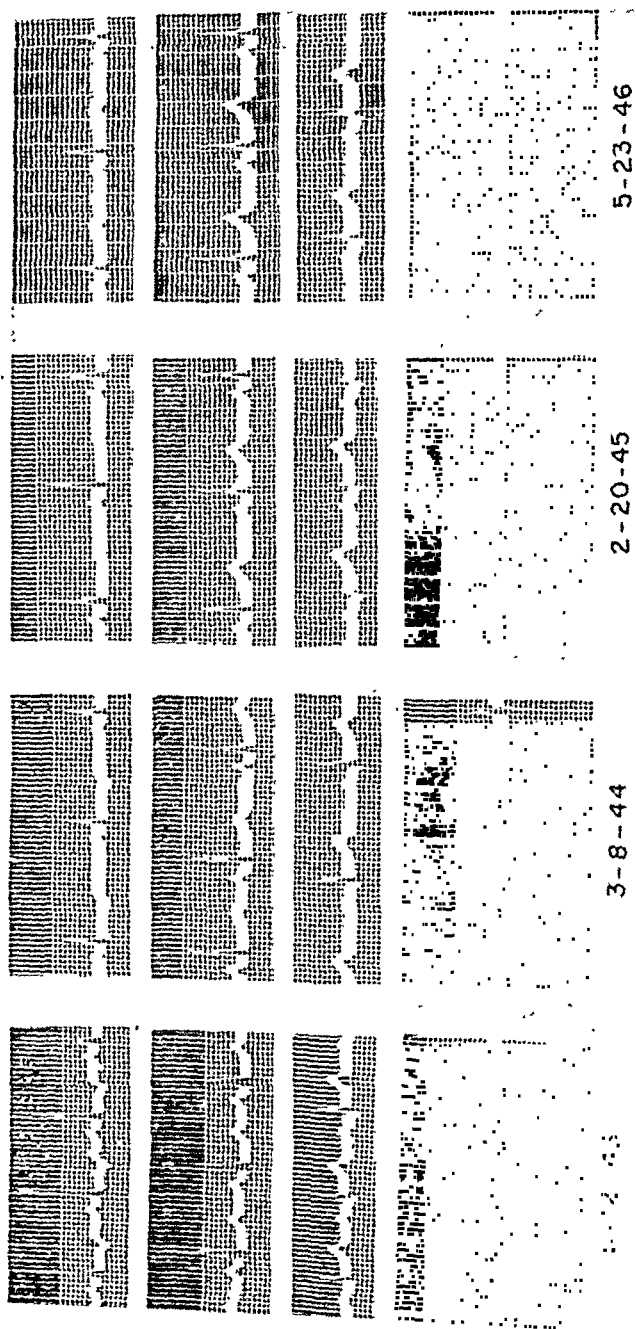


FIG. 13.

40 mm. Hg; reduction in heart size with change in the transverse diameter of 18 per cent or more; change in  $T_1$  from completely inverted to upright; disappearance of severe retinopathy.

I will begin with three typical cases of so-called benign essential hypertension without serious cardiac, renal or retinal complications.

The first one is an example of a satisfactory response to the diet in about four months. It is the case of a 35 year old woman who had had hypertensive vascular disease for 11 years. There was no evidence of any renal excretory involvement. Of two brothers with hypertensive vascular disease, one had died of a stroke at the age of 37. For years, the patient did not feel up to par with increasing fatigue and exhaustion. There was a sensation of pressure and throbbing in the back of the head and in the eyes. From January to April, 1947, because of the appearance of retinal hemor-



Reprinted from the *American Journal of Medicine*, 4, April, 1948.  
FIG. 15.

diet, the importance of the time factor becomes obvious: In 392 patients who followed the diet for four to 74 days (average 37 days), there was a definite lowering of the blood pressure in 62 per cent. In 385 patients who followed the diet for 75 to 1,150 days (average 149 days), there was a definite lowering of the blood pressure level in 81 per cent.

The third case with benign essential hypertension is an example of a satisfactory response to the diet in one month. It is the case of a man now 47 years old who was well until he was 37. In March, 1940, he was seen in the New York Hospital. The blood pressure was 165 to 200 systolic and 105 to 135 diastolic. A diagnosis of hypertensive vascular disease was

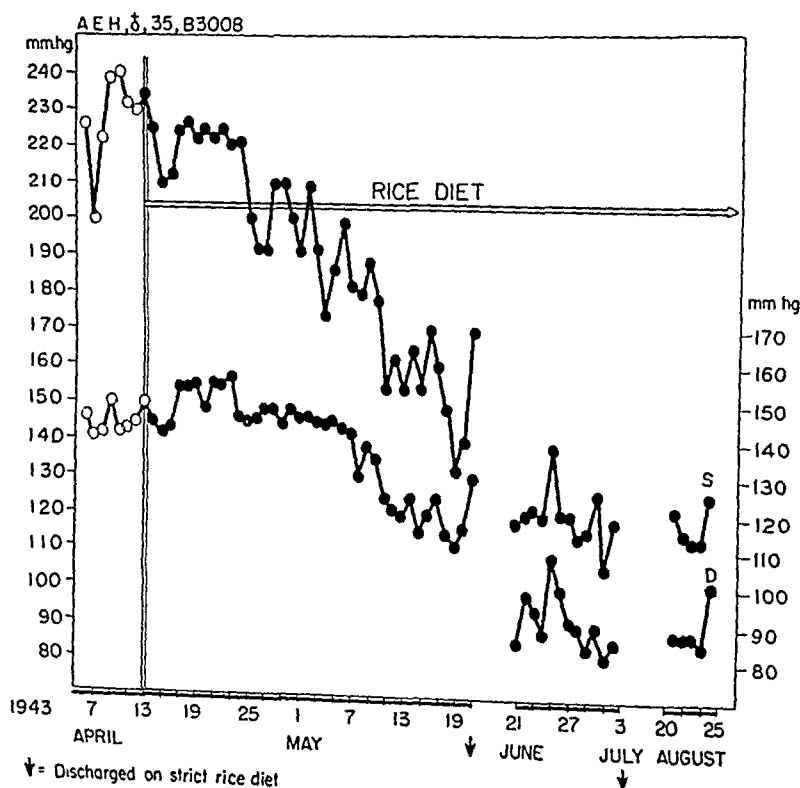


FIG. 16.

made. In January, 1941, he was seen in the Presbyterian Hospital. The blood pressure was found to be 200/140. One month later, the patient was seen in the Rockefeller Hospital with a blood pressure of 200/140. He was treated there by Dr. Henry Schroeder with tyrosinase until this had to be discontinued because of a severe shock-like reaction. As a matter of fact, this was the last patient whom Dr. Schroeder treated with tyrosinase. I like to show his record because Dr. Schroeder in the *American Journal of Medicine* in April of last year made the statement that the control periods preceding the rice diet might be too short to get an accurate base line for studying the effect of the diet. As is true for the majority of my patients, the base line for this patient was recorded by good observers not only over

are frequently told not to be concerned about their disease, unless some complication develops.

I believe the most appropriate time for treatment is before the more incapacitating complications of the disease have developed (cardiac breakdown, cerebral accidents, loss of vision and renal insufficiency). However, I will show you some typical electrocardiograms, chest films and eyeground photographs, which will illustrate that hypertensive vascular disease can be compensated to a great extent even when critical complications are already present.

Figure 14 shows the reversion of an abnormal electrocardiographic pattern to normal in a 35 year old man with hypertensive vascular disease of

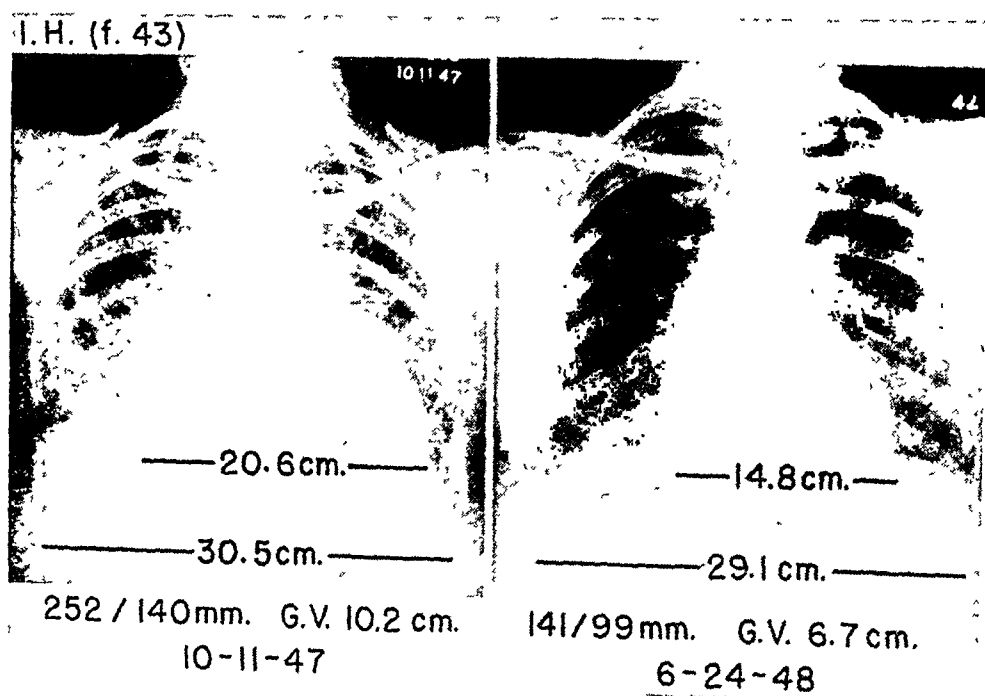


FIG. 18.

less than three years' duration. The change in the electrocardiogram is seen after 26 months on the rice diet. The blood pressure during this time decreased from an average of 205/122 to 150/103. Retinal hemorrhages and exudates disappeared. The deeply inverted  $T_1$  became upright; the electrical axis improved.

Figure 15 illustrates the time factor in the gradual improvement of  $T_1$ . The patient was a 35 or 36 year old woman. Hypertension was known to be present for about one year. In May, 1943,  $T_1$  was deeply inverted; in March, 1944,  $T_1$  was low inverted; in February, 1945, low upright; in May, 1946, normally upright. This case also shows that there is neither a simple relationship between blood pressure drop and  $T_1$  improvement nor between reduction in heart size and  $T_1$  improvement. The blood pressure decreased

from 220/150 to 124/85 (figure 16) and the heart became normal in size within 10 weeks on the rice diet. Three years were required for the inverted  $T_1$  to become normally upright.

Figure 17 shows the reversal of an inverted  $T_1$  in the shortest period of time we have seen, one month. It is the electrocardiogram of a 23 year old man with hypertensive vascular disease, uncomplicated for three years, in the malignant phase with severe neuroretinopathy for three months. During the first month of the rice diet in which  $T_1$  became normal, the blood pressure

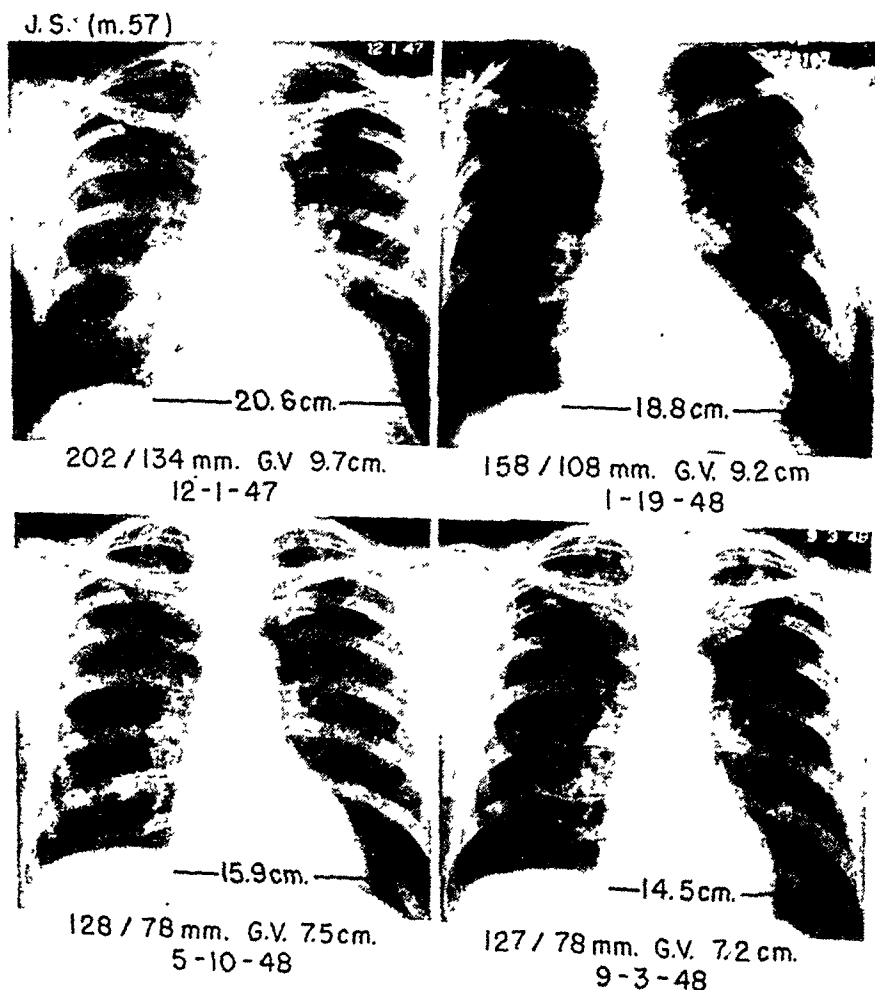


FIG. 20.

level decreased from an average of 222/148 to an average of 153/112. A normal blood pressure was reached only after two more months on the diet.

The T waves in Lead I were evaluated in 520 patients. None of these patients received digitalis or any other drug. All electrocardiograms were made with the patient at rest and in recumbent position. In 286 electrocardiograms which were normal at the start and in 102 electrocardiograms

disease had become apparent in April, 1947. It was treated with digitoxin, ammonium chloride, mercurials, nitroglycerin, aminophyllin, weight reduction, salt-restricted diet. In spite of this medication and a weight loss of 30 pounds, the blood pressure increased and the heart failure became worse. When the patient came to us, the rice diet was started, and all medication including digitalis was immediately discontinued. The edema disappeared in 20 days; the blood pressure returned to normal in two months (figure 19). A decrease in heart size was noted after six weeks with a change in the transverse diameter of 8.7 per cent; after five months there was a change of 29 per cent; after nine months there was a change of 42 per cent (figure 20).

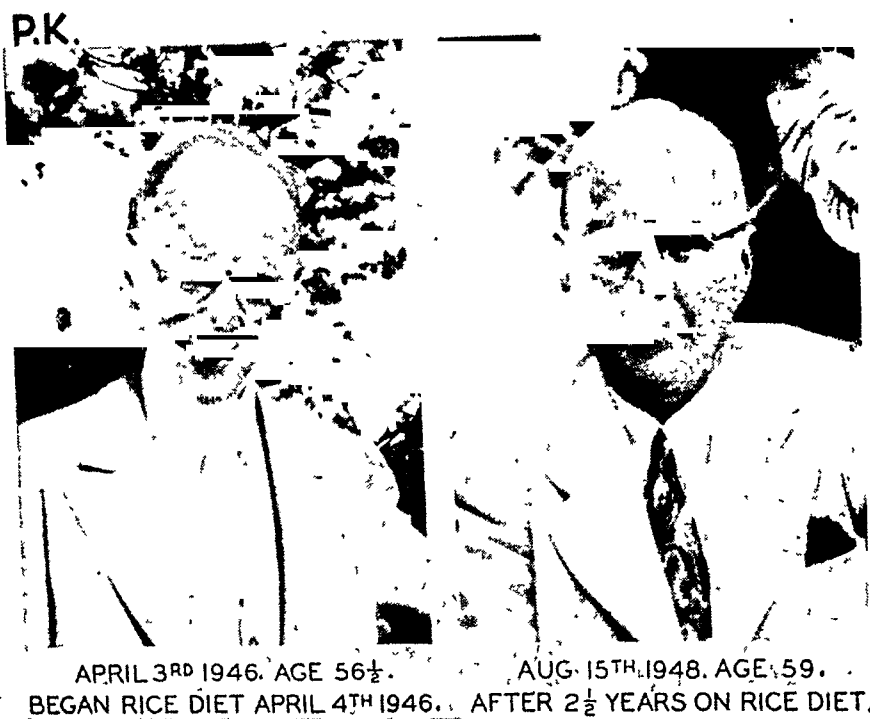


FIG. 22.

The patient became completely asymptomatic and has been without any medication for the past 14 months.

Chest films of 286 patients taken before and after one month or more of dietary treatment were measured for comparison (no digitalis or other drugs were given after the day the first chest film was taken). In 15 of the 286 patients (i.e. in 5 per cent), the heart became larger with an average increase of 2.6 per cent. In 146 patients there was a decrease in heart size with a change in the transverse diameter of 6.2 per cent (average), in 106 patients there was a decrease with an average change of 14.2 per cent and in 19 patients a decrease with an average change of 24.4 per cent (table 9).

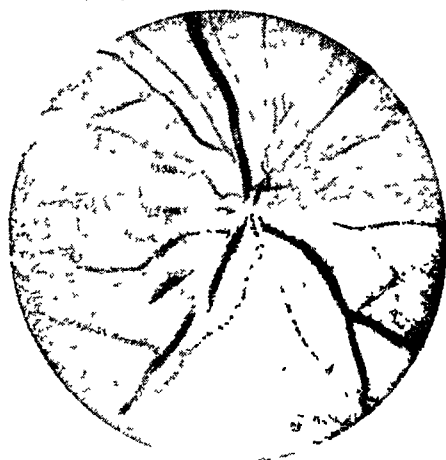
I do not think that the improvement in the electrocardiographic pattern or the decrease in heart size or the disappearance of papilledema, hemor-



the hope of arresting his vascular disease. In spite of this, the disease continued and a left bundle branch block developed. When heart failure gradually increased, digitalis, squill, mercupurin, ammonium chloride, sedatives and salt-poor diet were tried.

The first chest film of March 1946, showed a greatly enlarged heart. There was edema, liver enlargement, and ascites. All medication was immediately discontinued and the rice diet started. Five weeks later the transverse diameter of the heart was 3 mm. larger, but the patient had lost most of his edema and was no longer dyspneic. The patient ate one pound of rice (dry weight) and one pound of dextrose daily and gained over 7 kg. during

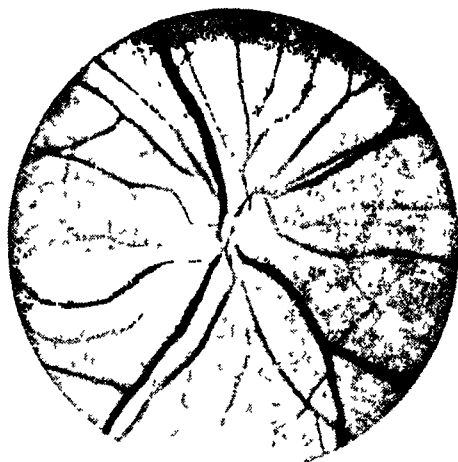
A.A.H (m, 47)



6-20-44

Blood pressure, average  
(June 20-July 20, 1944)

185/120



1-10-49

Blood pressure, average  
(January 10-11, 1949)

167/105

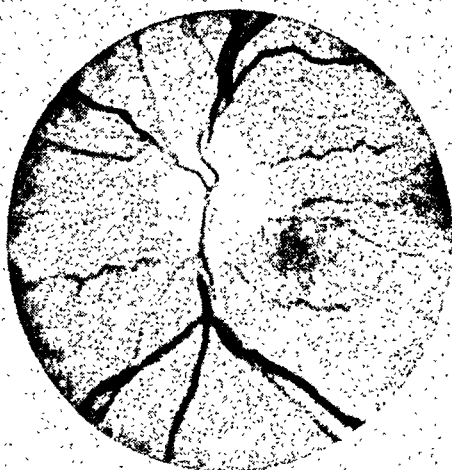
FIG 24.

seven months in spite of the loss of edema. Four months after the start of the diet the transverse diameter of the heart had decreased from 19.8 to 17.9 cm.; after seven months from 19.8 to 17.4 cm.; after 10 months from 19.8 to 16.5 cm. No medication has been given for the past three years. The patient is feeling well and is completely asymptomatic. The transverse diameter of the heart is now 16.3 cm., which means an overall change of more than 20 per cent. I showed the patient these heart pictures, boasting about the result. In return, the patient sent me a Christmas card with pictures of his face "before and after the rice diet" (figure 22). They are perhaps not uninteresting even from our mechanistic point of view. The first photograph shows the characteristic face of a patient with advanced heart disease,

P.M. (m. 51)



217/153 mm. 10-31-47



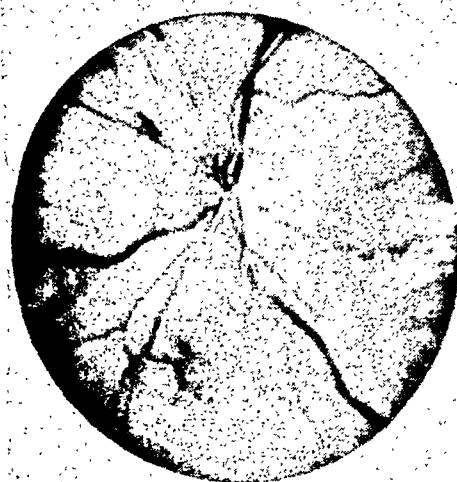
188/112 mm. 6-22-48

FIG. 26.

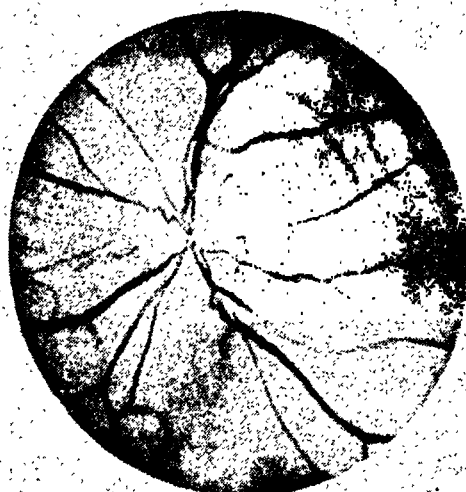
drawn, emaciated, prematurely aged, like that of a victim of starvation. The second photograph shows a well nourished, healthy man: one might say that the face has gained what the heart has lost.

Vascular retinopathy responds to the rice diet just as well as myocardial disease. The improvement of the retinopathy occurs no matter whether the blood pressure decreases or not.

L.W. (f. 45)



226/154 mm. 8-4-44

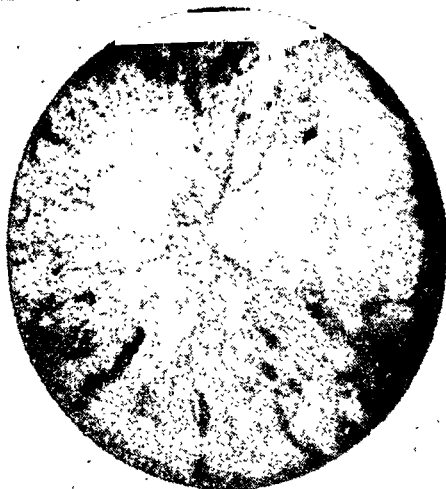


184/120 mm. 5-14-48

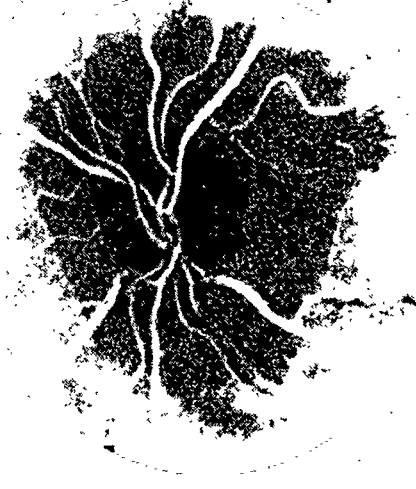
FIG. 27.

L.B. (f. 24)

LEFT



11-6-44



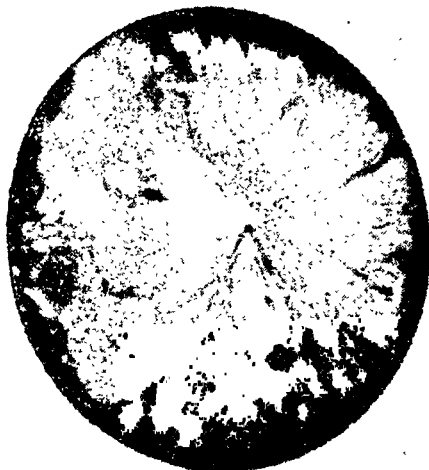
10-26-48

FIG. 30.

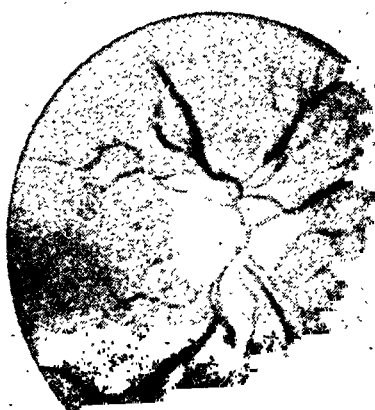
The second case is that of a man who was 47 years old when he came to us almost five years ago. He had been suffering from periodic attacks of severe headaches for years, but had known of his hypertension only for three months. He had not been conscious of any impairment of vision until I asked him to close his left eye and he found he was unable to read the headlines of a newspaper with his right eye. In one and one-half years of treatment with the rice diet, the exudates in the macula disappeared. The papilledema and hemorrhages cleared up completely and the eyesight was restored

L.B. (f. 24)

RIGHT



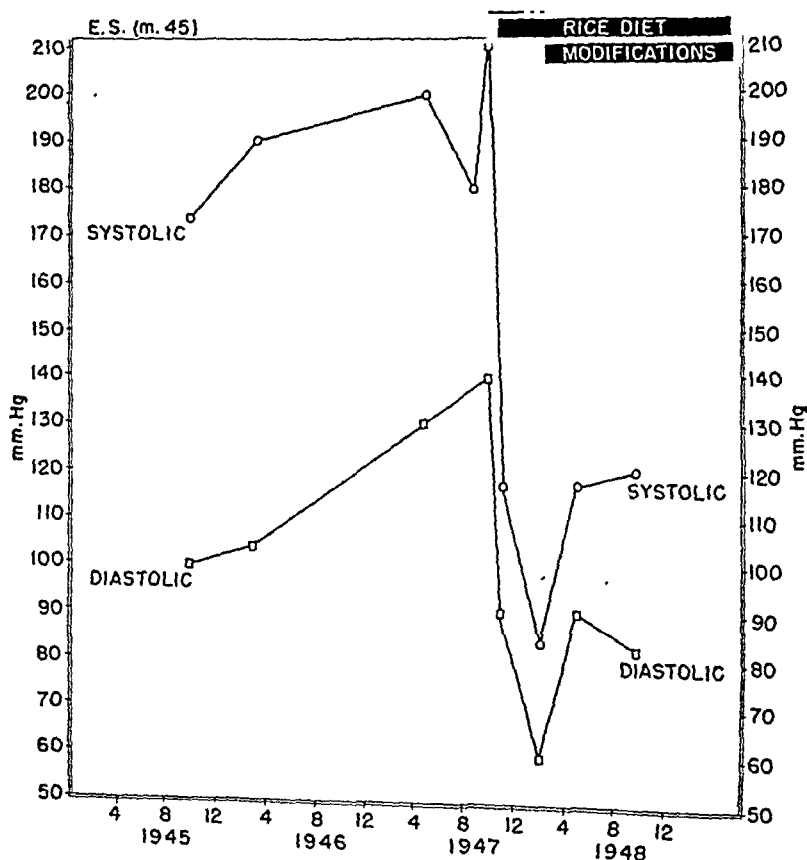
11-6-44



10-26-48

FIG. 31.

I have shown you pictures of patients who had essential hypertension with severe complications. We classify this type of hypertension as benign because of its slow course, although the term benign may lose its sense when the patient becomes blind from retinal disease or when he dies of heart failure, myocardial infarction, cerebral vascular accident or uremia. Moreover, the possibility always exists that any benign vascular disease may suddenly change into the malignant form. The last three patients whose eyeground photographs I showed you presented some of the signs said to be characteristic of malignant hypertension, the high diastolic blood pressure and



Reprinted from the *American Practitioner*, 3, May, 1949.

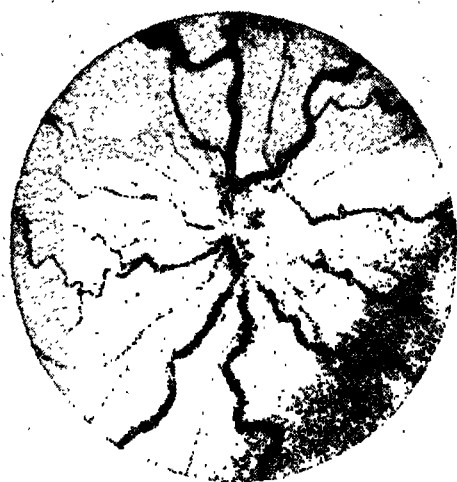
FIG. 34.

papilledema, hemorrhages and exudates. However, the eyegrounds did not show the picture of the explosive retinopathy which we associate with true malignant hypertension.

The following photographs are shown as examples of the effect of the rice diet on patients with full blown malignant hypertension.

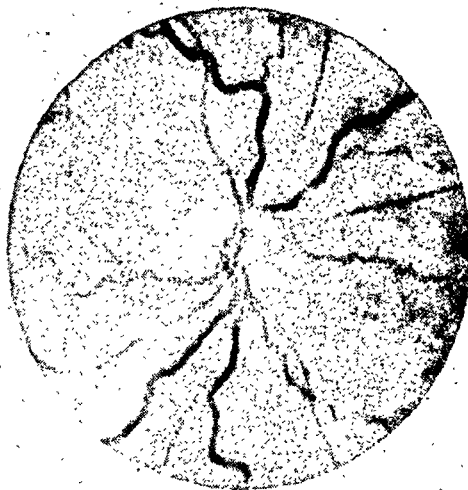
The first case is that of a 45 year old woman who came to us in 1944 with a history of hypertension of four months' duration, apparently malignant from the onset. The eyegrounds show the typical picture of malignant neuroretinopathy. The patient followed the strict rice diet for one

ness man from New York, had had periodic check-ups since 1932 when he was 30 years old. The blood pressure had always been normal until 1941 when a slight elevation was noted. It climbed slowly during the following years. In 1945, it was 170/100, in 1946 190/100, in the Spring of 1947 190/130. In spite of this, the patient was completely asymptomatic. Both family physician and consultant specialist advised treatment with weight reduction, rest, sedatives and restriction of smoking. In September, 1947, the patient suddenly developed a severe headache with visual disturbances and consulted an ophthalmologist who found retinal hemorrhages, exudates, and papilledema and made a diagnosis of retinopathy of malignant hypertension. Another medical specialist was consulted who found a blood pressure of 202/144, confirmed the diagnosis of malignant hypertension and sent



11-12-47

E.S. (m. 45)



9-2-48

Reprinted from the *American Practitioner*, 3, May, 1949.

FIG. 36.

the patient to a surgeon in the New York Hospital for sympathectomy. The surgeon made the same diagnosis and recorded the same findings. After eight days of observation, a sympathectomy was scheduled for Monday, October 27, 1947. The evening before the operation, the patient decided to try the rice diet first and came to Durham. He presented the typical picture of malignant hypertension. The blood pressure was 210/140, in spite of sedatives; the eyegrounds showed extensive neuroretinopathy. On the rice diet, the blood pressure decreased rapidly. As a matter of fact, it decreased so much that after three months the patient had a blood pressure of 85/58 while lying and 60/30 while standing. A marked hypochloremia with elevation of urea nitrogen and non-protein nitrogen was found and the diet had to be modified greatly by the addition of toast, meat and all kinds of vege-

# VIRAL HEPATITIS: PROBLEMS AND PROGRESS\*

By JOHN R. NEEFE, M.D., *Philadelphia, Pennsylvania*

THE problems associated with certain viral diseases of the liver have been the subject of intensive study during recent years. As methods permitting specific etiologic diagnosis are not available, the non-specific term "viral hepatitis" has been found useful for reference to the syndrome under consideration. "Viral hepatitis" thus includes those forms of hepatitis caused by hepatotropic, filterable, infectious agents which have not yet been identified with specific serological responses but which produce, as their outstanding manifestation, evidences of liver injury, which may or may not be associated with phenomena suggesting an infectious origin.

The available evidence indicates that at least two "virus-like" agents are concerned.<sup>1, 2</sup> One, hereafter referred to as virus IH, has been identified primarily with the clinical and epidemiological syndrome of infectious (epidemic) hepatitis. The other, hereafter referred to as virus SH, has been associated with the "homologous serum hepatitis" syndrome which characteristically develops two to five months after the occurrence of an opportunity for parenteral entry of the virus. The term "homologous serum hepatitis" really is an epidemiological term indicating the source of the infectious agent, but it unfortunately has acquired a misleading etiological implication in that the term has come to be synonymous with the hepatitis syndrome occurring after the long two to five month interval. However, virus IH also may be transmitted by blood or its products and be responsible for hepatitis after a two to six week interval. This syndrome also must be regarded as "homologous serum hepatitis," and it is therefore important to recognize that hepatitis syndromes occurring from two weeks to six months after exposure may be of viral origin and represent "homologous serum hepatitis."

The literature in recent years has been concerned almost entirely with the advances in knowledge concerning "viral hepatitis." It has seemed worthwhile, therefore, to refer briefly to some of the more important advances and then to devote the majority of the present discussion to a consideration of some of the remaining problems and current investigations directed toward their solution.

## RECENT ADVANCES

As the recent advances in knowledge concerning viral hepatitis have been reviewed in detail elsewhere,<sup>1, 2</sup> only those pertinent to the present discussion

\* Presented as a Morning Lecture at the Thirtieth Annual Session of The American College of Physicians, New York, N. Y., April 1, 1949.

From the Nutritional Service of the Gastro-Intestinal Section of the Medical Clinic and of the Department of Pediatrics, Medical School and Hospital of the University of Pennsylvania.

present time are characterized by certain clinical features which are more consistent with the clinical syndrome that was observed in association with hepatitis virus SH under experimental conditions. As these differences in the clinical syndromes of virus IH and SH hepatitis, as observed experimentally, have been described in detail elsewhere,<sup>1, 3</sup> the summary in table 1

TABLE I

Clinical Differences between Virus IH and Virus SH Hepatitis as Observed in Volunteers

Observation	Virus IH	Hepatitis Virus SH
1. Type of onset	Abrupt	Insidious
2. Constitutional symptoms with onset	Marked	Minimal
3. Fever with onset	Present	Absent
4. Laboratory evidence of hepatic injury in association with clinical onset	Delayed 2 to 7 days	Often present before clinical symptoms

will suffice for the present discussion. Although it must be *strongly* emphasized that these differences are *not* sufficiently reliable or consistent to permit their use for clinical differentiation between virus IH and SH hepatitis, the similarity between the clinical features of many sporadic hepatitis cases and those of the virus SH syndrome leads one to suspect that some of them may be due to this virus. Thus, in a spot survey of approximately 250 cases of "viral hepatitis" hospitalized during June 1947 in the United States Army Hepatitis Center at Bayreuth, Germany (120th Station Hospital), Dr. W. Paul Havens, Jr. and I were impressed with the fact that approximately 85 per cent of the patients had had a relatively silent, insidious, almost asymptomatic, afebrile onset of jaundice. This contrasted strikingly with the usual type of onset of the naturally occurring disease observed in this and other overseas theatres during the recent war, namely a sharp, febrile onset associated with marked constitutional symptoms. In addition, it was found that almost all of the cases hospitalized in the Center at that time were sporadic, only a small proportion of the total cases having arisen in association with small, localized outbreaks. Perhaps of some significance was the fact that almost every patient in this group had had some exposure to the "syringe-needle" source of hepatitis virus during the six month period prior to the onset of the disease.

It seems reasonable, therefore, to suspect that at least some of the cases of sporadic viral hepatitis may be due to virus SH.

The possibility of an etiologic relationship between viral hepatitis and certain etiologically obscure forms of chronic liver disease, such as those illustrated by the following brief case abstracts, also is of considerable interest and importance.

*Case N92-49.* A 19 year old white female had a silent, asymptomatic, afebrile onset of jaundice with minor gastrointestinal symptoms during the spring of 1948.

groups of young adults who previously had had either maximal or minimal exposure to hepatitis virus without having developed clinically recognizable infections. The incidence of such findings in both groups has approximated 10 per cent. It is hoped that continued observation of these groups over a period of years will help to clarify the significance of the present subclinical abnormalities.

*Epidemiology:* Little additional information concerning the epidemiology of naturally occurring outbreaks of viral hepatitis has been obtained during the past two years. The probable importance of contaminated water as a source of some outbreaks deserves further emphasis. Epidemiological and experimental evidence of the natural transmission of hepatitis virus IH by this means was first reported in 1945 by the author and Dr. Joseph Stokes, Jr.<sup>5</sup> Subsequently, additional outbreaks have been traced to this source on the basis of epidemiological evidence and very recently Drs. John Farquhar and Joseph Stokes, Jr.<sup>6</sup> have studied a localized rural epidemic in which epidemiological data provided strong evidence that the virus was transmitted by water from a contaminated well.

In respect to the problem of *blood transmitted hepatitis virus*, evidence of the probable importance of the asymptomatic carrier is slowly accumulating. We have previously reported circumstantial evidence indicating that such a carrier was the source of a hepatitis virus that was present in a pool of mumps convalescent plasma in which his plasma had been included.<sup>7</sup> Experimental studies have shown conclusively that hepatitis virus was present, at least intermittently, in the blood of inoculated volunteers during the long asymptomatic interval between inoculation and the onset of clinically recognizable symptoms and signs of the disease.<sup>8, 9</sup>

Of particular interest in this respect is the recent recognition by Drs. J. Edward Berk and Leonard Malamut<sup>10</sup> of a professional donor who may represent a true asymptomatic long term carrier of hepatitis virus. Three of their patients who had developed the syndrome of homologous serum hepatitis had received blood from this professional donor at different times over an eleven month period during 1947-48. One of these patients had received no other blood or plasma. The onset in all three cases was approximately six weeks after transfusion. Subsequently, it was found that a patient who had received his blood in 1945 (no other blood or plasma) had developed jaundice within three months, the exact interval not being certain. Thus at least four cases of homologous serum hepatitis may be traceable to blood obtained from this professional donor at different times over a three year period. The donor had no history of recognized hepatitis or other liver disease. However, study of the donor by Berk and Malamut revealed the presence of hepatic dysfunction and a liver biopsy provided histologic evidence of chronic liver disease with diffuse fibrosis. The rôle of the hepatitis virus in the donor's hepatic disease is not clear as he also was a chronic alcoholic. It is hoped that transmission studies with this donor's serum, which are planned by Drs. Joseph Stokes, Jr. and John Farquhar in



On the basis of these figures which do not include the cases of hepatitis without jaundice, there appears to be strong evidence of a serious risk in the use of large plasma pools and a smaller, but significant, risk in the use of either small plasma or whole blood pools. The risk of whole blood and small plasma pools often is increased by the frequent need for multiple transfusions by the same patient.

Unfortunately, the problems associated with hepatitis virus in blood extend beyond those involved in blood and plasma transfusion. The multiple opportunities for exposure to hepatitis virus of this origin are not generally recognized, the diagnosis frequently is not entertained in the absence of a history of transfusion, and some opportunities for prevention occasionally may be overlooked. It seems desirable, therefore, to cite some of the many potential sources of infection from blood:

1. *Purposeful parenteral introduction of blood or its products:*

- (a) Transfusions of blood, plasma, or serum.
- (b) Passive immunization with normal or convalescent blood, plasma, or serum.
- (c) Incorporation of plasma or serum into other biological products.
- (d) Therapeutic local application of blood or its products to open lesions.
- (e) Injection of certain products of human plasma fractionation.

2. *Accidental parenteral or oral introduction of blood or its products:*

- (a) Inadequately sterilized syringes, needles, lancets, and other instruments that come in contact with blood or its products and are used for:
  - 1. Intravenous, intramuscular, subcutaneous and intracutaneous injections (diagnostic, therapeutic and prophylactic procedures).
  - 2. Venous punctures for blood withdrawal only.
  - 3. Skin punctures (blood counts, other blood specimens, etc.)
- (b) Contamination of open skin and mucous membrane lesions or accidental ingestion of blood or its products through handling of blood specimens or blood-contaminated materials (excreta, wound discharges, etc.).

Contributing to the importance of the above sources is the fact that either IH or SH type virus may be present in blood and either the oral or parenteral route of entry therefore may be involved. Also pertinent to these considerations is the fact that in any infectious disease in which minute amounts of blood contain the agent, the possibility of mechanical or biological transmission by biting insects cannot be excluded. Although no definite evidence of transmission by biting insects has been obtained to date, a previously un-

"After a trial of more than one month and a verdict elaborated in sixteen hours, as reported in a previous letter, the physician of Varese who had been accused of disseminating by his imperfect technic an epidemic of 'syringe hepatitis' was sentenced to serve five years in prison, to discontinue practice for two additional years and to compensate the families of the victims, of whom 12 had died and an additional 100 were infected. The entire nation has been interested. The sentence seems terrible, for in 1946 nobody in Italy knew anything about infection with hematogenous hepatitis through imperfect sterilization of the syringe. The physician of Varese gave no less than 50 intravenous injections of a tonic to his patients every day.

"The trial had aroused the entire medical profession in Italy because the incriminated physician had an excellent reputation. The defense council will apply to the Court of Appeal, but for the moment the physician, who had enjoyed liberty conditionally, has been imprisoned."

Although it seems doubtful, on the basis of the evidence described, that the action taken in this case was justified, it serves to indicate the potential hazard involved.

As questions concerning the *control* of blood borne hepatitis virus frequently arise, it has seemed worthwhile to consider what preventive measures may be taken, on the basis of existing knowledge, in order to reduce the incidence of infections from this source.

I. *Detection of Infected Donors*: Such a preventive measure obviously would be of great value if it could be accomplished. Unfortunately, no practical method for rapid demonstration of hepatitis virus in blood has yet been developed. However, it appears that some infectious donors may present detectable evidence of clinical or subclinical hepatic injury. Such donors might be recognized by the routine performance of a relatively small group of laboratory tests. For this purpose, the following scheme is suggested:

1. Exclude donors with history of hepatitis or unexplained recent symptoms.
2. Physical examination with particular reference to liver.
3. Screening tests for hepatic disturbance:

*a. Before blood is drawn:*

1. Urine bilirubin.
2. Urine urobilinogen (sensitive simple methods are available).
3. Exclude donor if either test positive.

*b. After blood is drawn but before blood is released:*

1. Total and prompt direct reacting serum bilirubin.
2. Cephalin cholesterol flocculation test (24 hr.).
3. Thymol turbidity and flocculation tests.
4. Do not release blood if any of these tests positive.

promising hopes for this originate from recent observations which suggest that some viruses may be destroyed by small quantities of certain chemical agents which can be added to blood or plasma without serious alterations of these substances or danger to the human recipient of materials so treated.<sup>18</sup>

III. *Prevention of the Disease in Recipients of Blood and Its Products:* The ability of human immune serum (gamma) globulin to prevent virus IH hepatitis when injected in the incubation period prior to the onset of the disease was demonstrated in 1944 by Dr. Joseph Stokes, Jr. and the author.<sup>1, 19</sup> Its effectiveness has since been confirmed by other investigators in four additional epidemics occurring in widely separated areas both in this country and abroad,<sup>1, 2</sup> the most recent confirmation being provided by Drs. John Farquhar and Joseph Stokes, Jr. in an institutional epidemic occurring in 1948.<sup>6</sup> These investigators also obtained some evidence through this same study which suggested that persons who received gamma globulin during the incubation period, or were exposed shortly after receiving gamma globulin, experienced an inapparent infection which resulted in active immunization.<sup>20</sup> That such immunization can occur from subclinical infection has been demonstrated experimentally in studies previously reported by the author in connection with Dr. Sidney S. Gellis and Dr. Joseph Stokes, Jr.<sup>3</sup> In this study, volunteers who failed to develop clinically detectable signs of active infection after parenteral inoculation with virus IH were subsequently found to be resistant to oral challenge inoculation with highly active virus IH. The possibility of accomplishing active immunization by a proper combination of gamma globulin and attenuated hepatitis virus has been suggested by Dr. Stokes and this deserves prompt exploration and study.<sup>20</sup>

Unfortunately, the usefulness of human immune serum globulin in the prevention of virus IH infections apparently does not extend to virus SH infections,<sup>21</sup> which appear to be the most frequent problem associated with blood or plasma transmission. Although the studies to date indicate that even large and repeated doses of gamma globulin fail to prevent virus SH hepatitis, the fact that some blood transmitted infections are due to virus IH probably warrants the use of prophylactic injections of gamma globulin in association with multiple transfusions of blood and non-irradiated plasma. This also appears desirable as a prophylactic measure in recognized exposures occurring through the "accidental" mechanisms. In this respect, it seems desirable to emphasize the fact that careful follow-up studies of several thousand persons injected with gamma globulin have failed to reveal any evidence that this material itself has been a source of either virus IH or SH infections.<sup>21</sup>

IV. *Reduction of Incidence by Selection of Materials:* It is evident from the foregoing that none of the methods of prevention thus far described can be depended upon to eliminate the hazard of viral hepatitis at present inherent in the use of blood and certain of its products. Gamma globulin

1. Hepatitis virus in serum albumin solution was inactivated by heating at 60° C. for 10 hours.
2. Hepatitis virus in contaminated water was inactivated by "break-point" chlorination.

Neither of these studies provided information concerning the minimal requirements for inactivation of the virus by either method but they do indicate the susceptibility of hepatitis virus to inactivation by proper exposure to heat and chemicals. Obviously the presence of blood clots and other foreign materials tends to interfere with exposure of the hepatitis virus to disinfecting agents. Thus, proper and thorough cleansing of syringes, needles, and other instruments is of primary importance. If this is well done, it is probable that complete immersion in boiling water for five minutes would represent "adequate" sterilization. Likewise, if care is taken to insure complete contact of all surfaces of thoroughly cleansed syringes, needles, lancets, etc. with potent chemical disinfectants for at least one hour, it seems reasonable to assume that "adequate" sterilization would result. In my opinion, however, heat sterilization should be employed whenever possible and the autoclave would be the method of choice.

Prevention of infection from contact with blood or blood contaminated materials or objects involves precautions of such magnitude that special measures other than reasonable care appear justifiable only in respect to patients with recognized or suspected hepatitis.

#### SUMMARY AND CONCLUSION

"Viral hepatitis" is presented as a syndrome caused by at least two, primarily hepatotropic, filterable, infectious agents (Viruses IH and SH) which have not yet been associated with specific serological responses but which produce, as their outstanding manifestation, evidences of liver injury, with or without phenomena suggesting an infectious origin. Some of the major advances in knowledge concerning etiology, epidemiology, clinical aspects, and prevention are enumerated and certain of the remaining problems are discussed. The possible relationship of hepatitis viruses to certain etiologically obscure types of hepatic disease and the possible rôle of virus SH in the etiology of so-called sporadic hepatitis are considered. The problems associated with blood transmission of hepatitis viruses are reviewed and possible methods of reducing the incidence of infections from this source are considered. The data presented herein clearly indicate that many important aspects of the problem of viral hepatitis remain to be solved.

#### BIBLIOGRAPHY

1. NEEFE, J. R.: Recent advances in the knowledge of virus hepatitis, *Med. Clin. N. Am.*, 1946, 1407-1443, Philadelphia number.
2. HAVENS, W. P., JR.: Infectious hepatitis, *Medicine*, 1948, xxvii, 279-326.

# THE CLINICAL MANIFESTATIONS AND LABORATORY DIAGNOSIS OF RICKETTSIALPOX\*

By HARRY M. ROSE, M.D., *New York, N. Y.*

RICKETTSIALPOX, the newest member of the human rickettsioses, was first observed in 1946<sup>1,2</sup> and thus far has been confined exclusively to the metropolitan area of New York City. The etiological agent was identified by Huebner and his associates<sup>3</sup> as *Rickettsia akari*, a new species which is serologically related to the spotted fever group of rickettsiae. The disease is apparently transmitted to man by a blood-sucking mite, *Allodermanyssus sanguineus*, an arthropod parasite of rodents.<sup>4</sup> *Rickettsia akari* has been isolated from pools of these mites collected in dwellings where cases of rickettsialpox have recently occurred. The tropical rat mite, *Liponyssus bacoti*, has also been shown experimentally to be a potential vector,<sup>5</sup> although its rôle in the natural transmission of the disease is undetermined at the moment. An animal reservoir of the infection exists in the common house mouse, *Mus musculus*,<sup>6</sup> and the associated occurrence of rickettsialpox with the rodent infestation of dwellings has been well established.<sup>7</sup>

Rickettsialpox continues to be seen frequently in New York City, especially in upper Manhattan and the Bronx, although only a few cases have occurred in Brooklyn and none have been recognized on Staten Island. In the past three years nearly 500 cases have been reported to the Bureau of Preventable Diseases, New York City Department of Health,<sup>8</sup> and many others have undoubtedly escaped recognition, especially those of mild or atypical character. Since the spring of 1947, 35 proved cases of rickettsialpox have been seen at the Columbia-Presbyterian Medical Center of which 22 were admitted to the hospital and 13 were followed in the out-patient department. These cases furnish the basis for the present communication, which deals with the clinical manifestations of the disease and the methods employed in the laboratory for specific serologic diagnosis and for the isolation of the responsible agent. Brief reference is also made to the results of treatment with aureomycin in two patients and with streptomycin in one patient.

## CLINICAL MANIFESTATIONS

The general clinical features of rickettsialpox have been previously described.<sup>9</sup> The onset of the illness is usually characterized by the appearance of a primary cutaneous lesion at the site of inoculation by the arthropod vector. About a week later the patient develops fever, chills, malaise and

\* Presented at the Thirtieth Annual Session, American College of Physicians, New York, N. Y., March 30, 1949.

From the Departments of Medicine and Bacteriology, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.

*Age and Sex Incidence.* As in most infectious diseases which are unrelated to occupation, rickettsialpox has no predilection for either sex. In the present series of 35 cases, 18 were females and 17 were males. The ages of the patients ranged from two to 56 years.

Eighteen of the 35 cases occurred in persons of the negro race, a much larger proportion than would be expected among general admissions to this hospital. The high incidence among colored patients is probably a reflection of their economic status and the fact that their living quarters are usually poor and often heavily infested with mice.

*Primary Lesion.* In 29 of the 35 patients primary cutaneous lesions could be readily identified. These consisted of areas of erythema and in-



FIG 1. A typical late primary lesion. This lesion was situated on the right upper arm of a 15-year-old boy.

duration from 1.0 to 2.5 centimeters in diameter. At an early stage the lesions exhibited a central vesicle containing slightly cloudy or opaque fluid. In older lesions this vesicle had ruptured or undergone desiccation, leaving a dark brown or black crust which closely resembled the primary eschar described in *fièvre boutonneuse*, *tsutsugamushi* disease, and occasionally in cases of Rocky Mountain spotted fever. The lesion was slightly painful and tender in a few instances, but usually it produced no local symptoms and in several cases it had not been previously recognized by the patient. A typical late primary lesion is shown in figure 1.

Twelve patients had single primary lesions on either the arms or legs. The head or neck was the site in eight others, in one of whom it was situated

The outstanding feature of the individual lesion in most cases was the development of vesiculation, although it is important to point out that occasionally no vesiculation whatever was seen. In a number of instances the vesicles appeared only as small, pin-point, opaque areas at the summits of papules. More frequently, however, the vesicles were larger and often con-

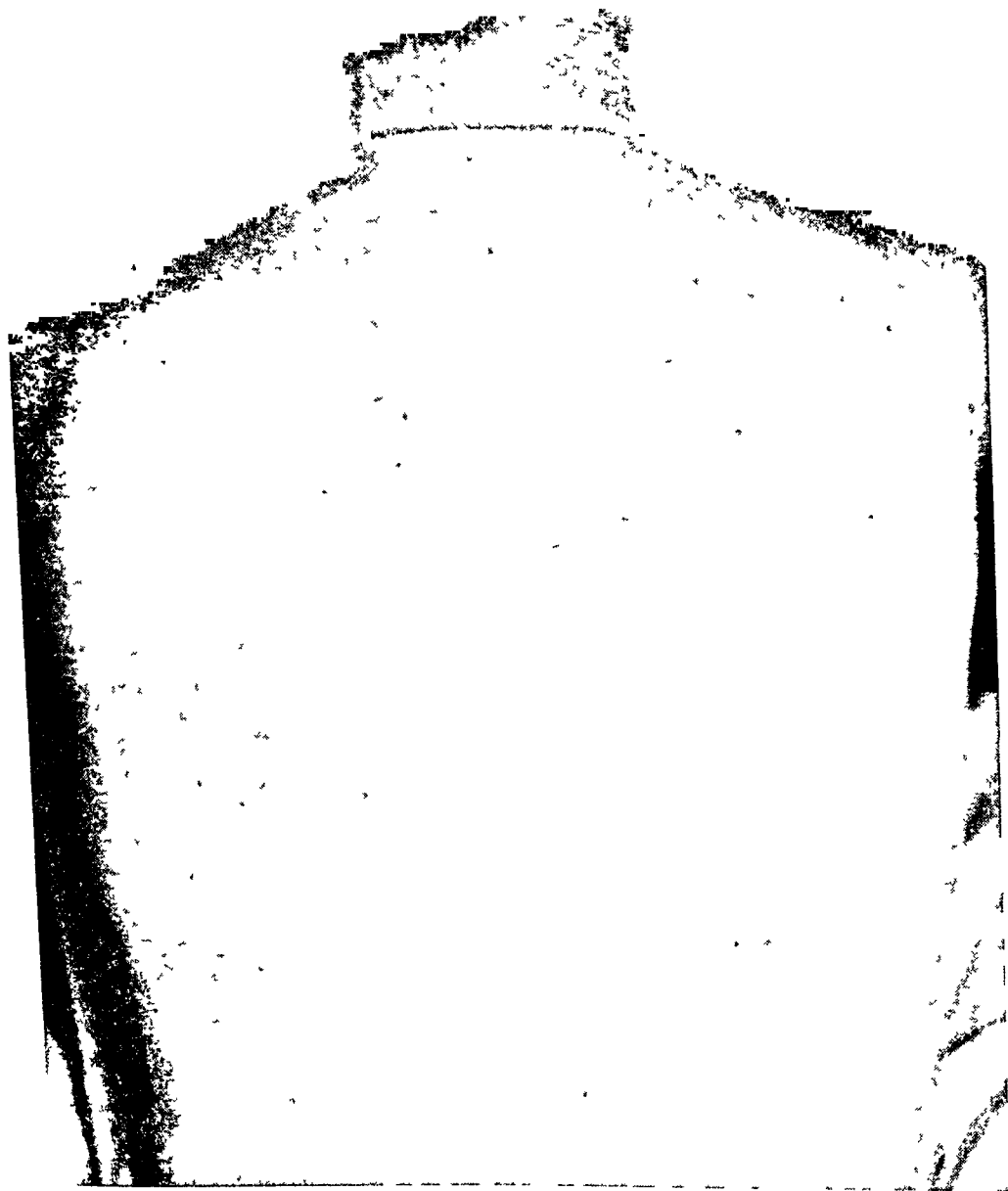


FIG 3. The typical secondary eruption of rickettsialpox in a 34-year-old man.

stituted the majority of the papule, being surrounded by a band of erythema. These latter vesicles were difficult to distinguish individually from those seen in chickenpox. The eruption was pruritic in several cases although in most patients it did not cause any discomfort and was never painful. As the eruption retrogressed blackish crusts formed at the sites of the larger vesicles.

ranging between 2,500 and 5,500 per cubic millimeter. Five patients had total counts from 6,000 to 10,000 and two patients had a slight leukocytosis, the maximum being 12,500 cells. The differential count was essentially normal in 22 patients and no abnormal leukocytes were seen in the stained smear. In six individuals, however, the smears showed a number of abnormal leukocytes—large mononuclear cells with vacuolated cytoplasm—similar to the peculiar cells usually seen in the blood of patients with infectious mononucleosis. Indeed, three of these patients were admitted to the hospital with a provisional diagnosis of infectious mononucleosis based in part on the hematological findings. The abnormal mononuclear cells did not tend to persist in the blood and were present for only a day or two; their significance is undetermined. Tests for heterophile antibody never showed a significantly elevated titer of sheep cell agglutinins, either during the acute illness or in convalescence.

Rickettsialpox is similar to Q fever, among the group of rickettsial infections, in that the Weil-Felix reaction is negative. Agglutinative tests with Proteus OX19 and OXK were done with the acute and convalescent phase serums of 13 patients and in no instance was a positive result obtained although low titers of agglutinins were observed in a few cases.

The serums of a number of patients were also tested for cold agglutinins against Group O human erythrocytes and in none were the titers significantly elevated.

Examinations of the cerebrospinal fluid in the three patients previously referred to were completely negative.

*Specific Serologic Diagnosis.* In recent years serologic methods have been developed for the precise diagnosis of rickettsial infections. The method most widely employed is the complement fixation test, using antigens prepared from rickettsiae grown in the yolk sacs of chick embryos. One type of antigen consists of washed, concentrated rickettsial suspensions from which the chick tissue has been largely removed by flocculation and differential centrifugation.<sup>11</sup> Another type is the soluble antigen which is released into the aqueous phase when saline suspensions of infected yolk sacs are shaken with ether.<sup>12</sup> This soluble antigen gives specific reactions, is easy to prepare and can be obtained from all species of rickettsiae except *Coxiella burneti*, the causative agent of Q fever.<sup>13</sup> In performing complement fixation tests for diagnosis the principle adhered to, if possible, is simultaneously to test two serums, one obtained in the acute phase of the illness and the other in convalescence, from two to six weeks later. The demonstration of the appearance of antibody, or of a significant rise in antibody titer, in the convalescent serum, establishes the temporal relationship of the specific immune response to the illness and thereby enables a retrospective diagnosis to be made. If no acute phase serum has been obtained, as in cases where the patient is first seen after the disease has subsided, the examination of a convalescent specimen alone may still give information of diagnostic value.



fixation tests with all three antigens. The serological relationships of *R. akari* are of great interest and are under further study at the present time.

Complement fixation tests were also done on the serums of three patients collected 9, 10 and 15 months, respectively, after infection. Moderately elevated titers of antibody were still demonstrable in each instance, indicating that the immune response is of fairly long duration, a phenomenon that has been shown to occur in other rickettsial diseases such as murine typhus<sup>14</sup> and Q fever.<sup>15</sup> The persistence of detectable antibody for many months after all clinical signs of the disease have subsided is of some practical significance in attempting to make a long-range retrospective diagnosis in certain cases.

TABLE I

Cross Reactions in Complement Fixation Tests with Serums of Cases of Rickettsialpox

Case	Day after Onset	Rickettsialpox Antigen	Spotted Fever Antigen	Murine Typhus Antigen
R. S.	6 24	0 64*	0 64	0 0
E. M.	7 45	0 128	0 32	0 8
H. R.	1 24	0 64	0 128	0 16
L. W.	4 30	16 64	0 16	0 8
L. A.	6 21	0 64	0 128	0 0
A. W.	8 26	16 128	32 64	16 16
A. J.	4 12	0 16	8 32	0 0
H. S.	6 37	0 256	0 32	0 0

\* Figures are reciprocals of the highest serum dilutions giving at least 2 + fixation with the respective antigens.

*Isolation of the Etiological Agent.* Attempts were made to recover the etiological agent in 10 patients by inoculating blood collected early in the disease intraperitoneally into mice, guinea pigs and into the yolk sac of chick embryos. From eight of these patients *R. akari* was isolated in the mice and from one individual the organism was also isolated directly in chick embryos. No primary isolations were successful in guinea pigs. The method employed was to inject a group of 8 to 10 Swiss mice each intraperitoneally with 0.5 to 1.0 c.c. of defibrinated blood freshly collected from the patient. Blood clot triturated with sterile bacteriological broth also proved to be a satisfactory inoculum. If animals were not immediately

virulence while others are highly pathogenic with LD50 titers exceeding  $10^{-5}$ .

From infected mice on the primary or later passages, *R. akari* were readily transferred to chick embryos. Suspensions of liver and spleen were inoculated into the yolk sacs of seven day old embryos which were then incubated at 35° C. The embryos died from four to nine days later, depending on the size of the inoculum, and numerous rickettsiae were demonstrated in the smears of the yolk sacs stained by the Macchiavello method. Once established, the strains could be maintained indefinitely in chick embryos by serial passage. Studies of one strain have shown that its pathogenicity for mice remained unimpaired through six consecutive transfers in eggs.

### TREATMENT

Rickettsialpox is a non-fatal disease and therefore the need for specific therapy is not as urgent as it is for other rickettsial infections such as typhus and spotted fever. Nevertheless, the unmodified infection may cause severe constitutional symptoms and the patient may be acutely and uncomfortably ill for a few days to a week or more. Certain antibiotics, including streptomycin,<sup>16</sup> chloromycetin<sup>17</sup> and aureomycin<sup>18</sup> have been shown to exercise a rickettsiostatic effect in chick embryos and experimental animals, while both aureomycin and chloromycetin have recently been demonstrated to have a remarkable therapeutic action in human rickettsial infections.<sup>19</sup> We have treated one case of rickettsialpox with streptomycin in a dosage of 0.5 gm. every six hours, but the drug apparently failed to influence the natural course of the disease. More recently, two patients were treated early in the disease with aureomycin in a dose of 1.0 gm. every six hours by mouth. In each of these cases the temperature fell precipitously to normal within 24 hours, accompanied by a rapid defervescence of symptoms and fading of the cutaneous eruption. The results of aureomycin therapy in human infections with *R. akari* will be reported in more detail elsewhere.

### SUMMARY

Rickettsialpox is a novel rickettsial infection of relatively mild character which thus far has not been observed beyond the environs of New York City.

The clinical and laboratory features of the disease have been described together with means for specific serologic diagnosis and isolation of the etiological agent.

### BIBLIOGRAPHY

1. SUSSMAN, L. N.: Kew Gardens' spotted fever, New York Med., 1946, ii, 27-28.
2. SHANKMAN, B.: Report on an outbreak of endemic febrile illness, not yet identified, occurring in New York City, New York State Jr. Med., 1946, xlii, 2156-2159.
3. HUEBNER, R. J., STAMPS, P., and ARMSTRONG, C.: Rickettsialpox—a newly recognized rickettsial disease. I. Isolation of the etiological agent, Pub. Health Rep., 1946, lxi, 1605-1614.

- LENNETTE, E. H., MEIKLEJOHN, G. and THELEN, H. M.: Treatment of Q fever in man with aureomycin, *Ann. N. Y. Acad. Sci.*, 1948, li, 331-342.
- COOKE, C.: Rocky Mountain spotted fever treated with aureomycin, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 885.
- ROSS, S., SCHOENBACH, E. B., BURKE, F. G., BRYER, M. S., RICE, E. C., and WASHINGTON, J. A.: Aureomycin therapy of Rocky Mountain spotted fever, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 1213-1216.
- HARRELL, G. T., MEADS, M., and STEVENS, K.: "Aureomycin," a new orally effective antibiotic, *South. Med. Jr.*, 1949, xlii, 4-13.
- SCHOENBACH, E. B.: Aureomycin therapy of recrudescent epidemic typhus (Brill's disease), *Jr. Am. Med. Assoc.*, 1949, cxxxix, 450-452.

found with a frequency twice as high as in the younger group.\* When analyzed by individual decades, no significant variation was found. Pulmonary emboli, on the other hand, manifested a marked statistical increase beyond 70 years of age. It should be noted that while the incidence of arteriosclerosis in the age group 60 to 69 was equivalent to that found in the older decades, the incidence of pulmonary embolism was considerably less. As was anticipated, the incidence of arteriosclerosis was found to rise sharply until age 60. Beyond this age, the incidence was too high to permit useful comparison by decades.

In table 2 the data were correlated with the pathologist's final diagnosis. Cardiac thrombosis was found with greatest frequency (28 per cent) in the cardiovascular group and peripheral thrombosis was noted in 20 per cent of the 101 cases comprising this group. In the 18 patients constituting the hepatic disease group, cardiac thrombosis occurred in five cases and periph-

TABLE I

Age	Total Number of Cases	Thrombi	Pulmonary Emboli	Atherosclerosis
Under 50	20	3 15%	1 5%	10 50%
50-59	32	11 34%	1 3%	24 72%
60-69	56	21 41%	5 9%	52 93%
70-79	58	21 40%	11 21%	56 96%
80-89	36	12 36%	8 23%	33 92%

eral thrombosis in two cases. Pulmonary embolism occurred in from 10 to 20 per cent of all disease groups with the startling exception of cases of portal cirrhosis. In the 18 cases of portal cirrhosis, there was not one instance of pulmonary embolism. No extrapulmonary embolus was discovered in the hepatic disease group with the possible exception of one doubtful case. In no other disease group analyzed were emboli so totally lacking.

The failure to demonstrate emboli in the patients with liver disease led us to examine the autopsy protocols of other cases bearing a final diagnosis of Laennec's cirrhosis. Seventy-nine additional consecutive cases of Laennec's cirrhosis examined at autopsy were analyzed. In 17 of the 79

\* This report is based on autopsies conducted according to the routine established in the laboratory. It is probable that if special dissections of the lower limbs were made the incidence of peripheral thrombosis would be higher than is recorded in this paper. Nevertheless, since the necropsies were all performed according to the same technic, a comparison of incidence in the different groups is valid. In each case dissection of the pulmonary arteries was carried out in the same routine manner.

mechanism is usually disturbed in chronic liver disease.<sup>5</sup> It is unlikely that the prothrombin time delay frequently seen in cirrhosis of the liver could inhibit embolization without preventing peripheral thrombosis. In the older age groups the blood has also been found to be hypocoagulable<sup>8</sup> and liver function tests in the aged have frequently been demonstrated to be abnormal even in the absence of clinically demonstrable liver disease.<sup>5</sup> Nevertheless the data show a striking increase in the incidence of pulmonary thromboembolism beyond 70 years of age. We are led to conclude, therefore, that factors other than simple hypocoagulability may influence the incidence of pulmonary embolism.

This belief is strengthened further by the observation that certain cases of the migratory type of thrombophlebitis seem almost never to yield emboli while others clinically indistinguishable from the former variety, are frequently accompanied by pulmonary embolization. The first type of migratory thrombophlebitis may continue for many months, manifesting frequent fresh lesions without endangering the host with emboli to the lungs.<sup>6</sup> In the latter, pulmonary embolism may occur with startling frequency during the course of the disease.<sup>7</sup> These two types can be further distinguished by their response to anticoagulants. The embolizing type can be controlled by adequate anticoagulant therapy while the non-embolizing type sometimes cannot.

#### SUMMARY AND CONCLUSIONS

In 184 consecutive miscellaneous cases, excluding liver disease, the incidence at necropsy of pulmonary embolism was 14 per cent.

In 97 instances of portal cirrhosis, no pulmonary emboli were found. The incidence of cardiac and peripheral venous thrombosis in these 97 cases of liver disease was not significantly different from that of the miscellaneous group.

Since decreased coagulability of the blood is accompanied by reduced embolization in some instances (cirrhosis of the liver) and by increased embolization in other instances (aged patients), factors other than changes in coagulability of blood must be sought to explain the occurrence of pulmonary embolism.

*Acknowledgment:* The authors wish to thank Dr. Julius Rosenthal for permission to study the protocols of the cases described in this paper and to use the material for publication.

#### BIBLIOGRAPHY

1. JORPES, J. E.: Heparin in the treatment of thrombosis, 2nd Ed., 1946, Oxford University Press, London, page 149.
2. KNAUER, J. G.: Acute cor pulmonale: discussion of literature and report of case successfully treated with oxygen, *Bull. Am. Acad. Tuberc. Phys.*, 1939, iii, 36.
3. BARNES, A. R.: The problem of pulmonary embolism, *West. Jr. Surg.*, 1942, 1, 551.

# CHEST X-RAY SURVEYS IN GENERAL HOSPITALS, A CRITICAL REVIEW \*

By KATHARINE R. BOUCOT, DAVID A. COOPER, F.A.C.P., E. WAYNE MARSHALL, and FRED MACD. RICHARDSON, *Philadelphia Pennsylvania*

ROENTGENOGRAPHIC chest surveys of general hospital populations are fairly recent innovations. In 1936, Hodges<sup>4</sup> reported a chest x-ray survey of 1101 admissions to the University of Michigan Hospital. He found roentgen evidence of intrathoracic lesions in 90, or 8.1 per cent of those patients. Examination of their subsequent hospital records revealed 14 instances in which pulmonary pathology found on the survey films had not been recognized clinically. This represented an incidence of 1.5 per cent. Also in 1936, Pohle et al.<sup>8</sup> reported 1460 hospital admissions with normal lungs on physical examination. In 34, or 2.3 per cent of this group, x-ray evidence of pulmonary tuberculosis was present, and in four, or 0.3 per cent, active reinfection tuberculosis was suspected. In 1940, Plunkett and Mikol<sup>7</sup> reported x-raying 4853 admissions to 14 general hospitals in upstate New York and in 128, or 2.6 per cent, evidence of reinfection tuberculosis was found. No clinical data were presented in this series.

During the past 10 years, marked technical improvements have made available a miniature chest photofluorographic technic which was widely used by induction centers, the armed services, and large industrial plants during the war. With this background of previous experience, the United States Public Health Service and local health agencies have sponsored mass chest surveys in various localities throughout the United States.

The first report in the literature on the use of photofluorography in hospital surveys appeared in 1941. Douglas and Birkelo<sup>2</sup> reported examining 4727 prospective mothers on 4 by 5 film. In 29, or 0.61 per cent, roentgen evidence of active tuberculosis was discovered.

The first use of photofluorography as a *routine* hospital procedure appeared in April, 1942, when Hodges<sup>5</sup> analyzed 7841 patients admitted to the University of Michigan Hospital during a four month period. He found that 732, or 9.3 per cent, required more comprehensive x-ray study. Again there was no report of clinical follow-up on the group.

In 1945, Scatchard and Duszynski<sup>9</sup> reported the results of a chest survey made on 1832 admissions to the Edward J. Myer Memorial Hospital of Buffalo during the two and one-half summer months of 1944. Of these, 36, or 1.4 per cent, were found to have previously unsuspected pulmonary tuberculosis. Ten of the 36 cases had either been x-rayed previously and found negative or had not been x-rayed on previous admissions. The remaining 26 had never before been seen at the hospital. Further, in 1107 of these

\* Received for publication March 30, 1948.

1. *Location.* Three of the four units were well located adjacent to receiving wards. The fourth unit was adjacent to the entrance for private patients and visitors.

2. *Lay-out.* Not one of the four units had a suitable lay-out. All four had inadequate space and none had a waiting room. Two units had no dressing rooms, one unit had two, both of which were poorly ventilated, and the fourth had three cubicles. Only one unit had its own developing room and that room was so small that the dryer had to be placed where it interfered with the free access of patients and technicians to the unit itself. It is apparent that these survey units had been set up in odd available space rather than as carefully planned adjuncts to the admission departments.

3. *Procedure.* No adequate system insured that all admissions report to the unit, but arrangements at one hospital were such that no patient was discharged without having received a photofluorogram. Two units arranged for the technicians to receive a daily list of admissions against which that day's photofluorograms were checked. An effort was then made to have those missed on admission report to the unit. However, by the time this list reached the wards, some of the cases were unable to be moved. No unit operated around the clock nor over week ends. No unit operated on definite shifts to cover evening admissions.

Photofluorograms were developed and read daily at three of the four units. Reports from these units were promptly appended to hospital charts. At the other unit, the system was uncertain, the impression being gained that film rolls were cut when sufficient exposures had been made and read when some member of the x-ray department could be found who was not too busy to read them.

Film-reading was done at one unit by a part-time certified roentgenologist reading daily the films taken the previous day. At a second unit four Fellows in Roentgenology took turns at daily film-reading. Films at the other two units were read by any one of the roentgenologists available at the time the films were developed. At one unit reports were sent to the wards within 24 hours of the film-reading. At a second unit the photofluorograms were stapled to the reports and these sent to the wards promptly. At neither of the other two units was there a definite system though one of these made a charge of \$1.00 per photofluorogram for both private and ward patients. The roentgenologist in charge of this unit explained that ward cases could receive reductions in this as in other charges by consulting the Social Service Department. No other unit made any charge for photofluorographic services.

4. *Staff.* The largest hospital, with 53 average daily admissions, had two full-time registered technicians and a full-time clerk operating the unit, a clerk and a secretary full-time at the unit office, a nurse and a nursing supervisor full-time for follow-up, a certified roentgenologist part-time for daily film-reading, and a part-time chest specialist as supervisor.

graphic station, 14 by 17 retakes were subsequently made on 416 of the 1257 individuals read as having significant survey findings and on 261 of the 7442 negative cases. The study revealed that, of the 261 cases read "negative" by survey who incidentally had subsequent 14 by 17 films, 50, or 19.1 per cent, had pathology. Of these 50, only 23 of the retakes were chronologically sufficiently close to the survey film to be considered survey errors. Of the 416 retakes on survey cases thought to reveal significant pathology, the survey impression was confirmed in 290 and altered in 126. There was no organized clinical follow-up.

As far as could be determined no follow-up procedures were in practice at the remaining two units.

### DISCUSSION

Although hospital surveys are widely advocated, it appears that their ultimate purpose and fundamental philosophy are not clearly appreciated. The primary purpose of hospital chest surveys is not diagnostic, but is the detection of infectious tuberculosis in order to protect hospital personnel and other patients. This achievement is accomplished only by prompt diagnosis with isolation and appropriate treatment of cases uncovered by survey. If properly conducted, surveys of this type become an important adjunct to the tuberculosis control program of the community.

The concept of surveys as screening processes is of the greatest importance. Such a concept suggests that a significant percentage of cases whose films are read as "probably tuberculous" should ultimately prove to be non-tuberculous. No film should be read as revealing non-tuberculous pathology in a patient who is subsequently proved to have tuberculosis. This is one way of stating that a properly read hospital survey should be "overread" from the viewpoint of tuberculosis. Such an approach requires considerable indoctrination of survey film readers.

If hospital surveys are to be effective, a very high percentage of patients must report for photofluorography *at admission*. It is obvious that x-ray at discharge cannot protect contacts and often does not even lead to accurate diagnosis and therapy for the patient himself, viz. the following case report:

A 37-year-old white female, a private patient admitted in active labor March 31, 1947, received a 70 mm. photofluorogram at discharge 10 days post-partum. The film was read as revealing bilateral tuberculosis. The report was sent to her obstetrician who advised the patient to consult a chest specialist. The patient failed to follow this advice. On February 9, 1948, ten months post-partum, a 14 by 17 film taken because of 102° temperature, emaciation, dyspnea, etc., revealed far advanced tuberculosis with bilateral giant cavitation and soft infiltrations throughout the balance of both lungs. The baby was found to have an active tuberculosis at the right base, the husband to have a minimal lesion of indeterminate activity and a maid's film was read as suspect.

This case of active tuberculosis had been in the Maternity Division for 10 days undiagnosed and unisolated. Photofluorography at discharge had



unit was not in operation. At this hospital, during October, 1947, 1011 individuals were admitted during hours when the unit was closed. Of these 495 were too ill to report to the unit at the time they were subsequently sent for. This suggests that an important reason for failure to x-ray all admissions lies in the fact that the unit was not open around the clock.



FIG. 2. A. G., on February 9, 1948, ten months post-partum, a 14 by 17 film taken because of 102° temperature, emaciation, dyspnea, etc., revealed far advanced tuberculosis with bilateral giant cavitation and soft infiltrations throughout balance of both lungs.

One of the four units had a satisfactory follow-up program but even this was not fully effective in actual practice. It is obvious that, in the setting up of these four units, provision was made primarily for the taking and reporting of films. Record-keeping was seriously inadequate at all four units so that it was not possible to evaluate the real service rendered by these units to their respective hospitals and to the community.

and out-patients to the unit should be placed at the admission desk and the central Out-Patient Department registration desk. Some device for conspicuous marking of admission and clinic cards should be used in order that no patient be admitted to the ward, private room, or to a clinic without having received a photofluorogram. At the most successful unit studied such a

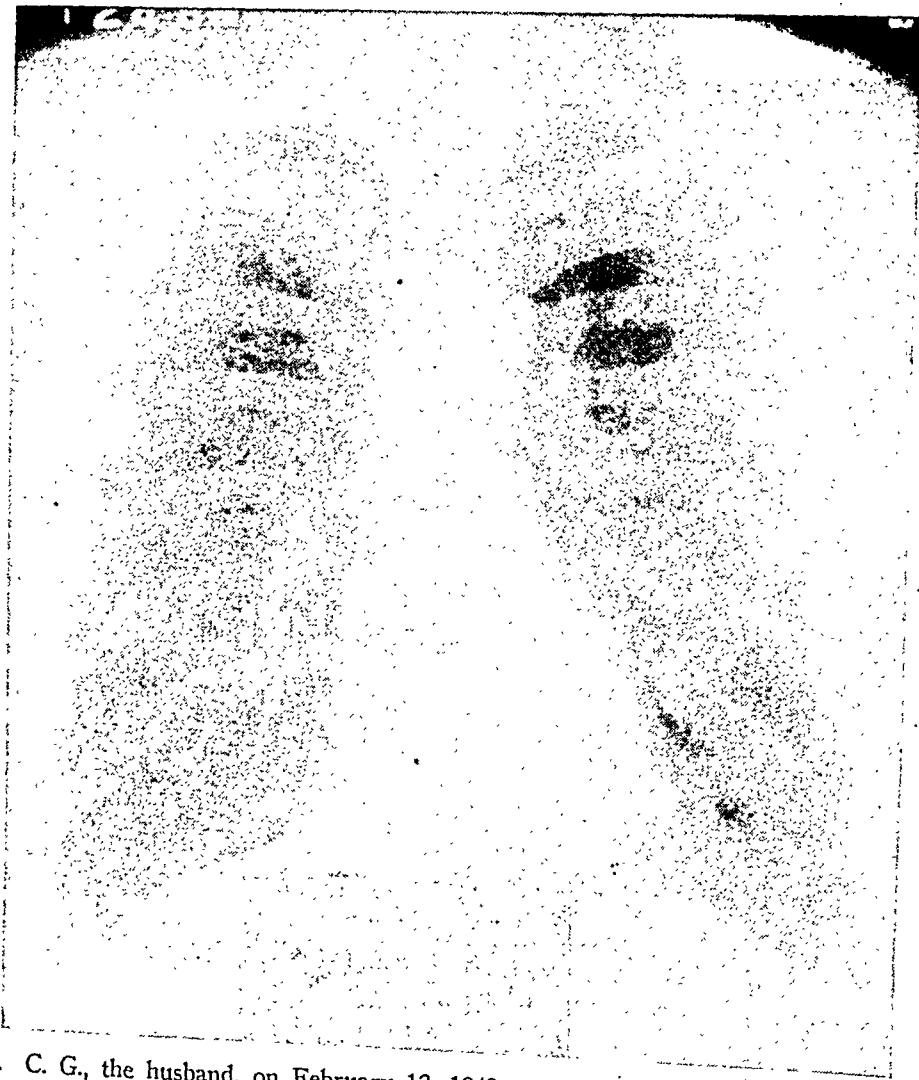


FIG. 4. C. G., the husband, on February 12, 1948 was found to have a minimal lesion of indeterminate activity at the left apex and first interspace.

device consisted of a 3.5" by 4.25" hollow "X" stamped in bright green directly over the admission or clinic card. This does not interfere with reading the data over which it is stamped.

4. Provision should be made for the taking of photofluorograms around the clock seven days a week. It is not necessary that a registered technician be on duty nights and weekends. A system should be set up for inclusion within the program of those patients who cannot be x-rayed on admission:

# CASE REPORTS

## DEATH DUE TO PARATHION, AN ANTICHOLINESTERASE INSECTICIDE \*

By DAVID GROB, M.D., WILLIAM L. GARLICK, M.D., GEORGE G. MERRILL, M. D.,  
and HENRY C. FREIMUTH, Ph.D., *Baltimore, Maryland*

THE introduction in recent years of anticholinesterase (antiChE) compounds as insecticides has led to problems arising from their toxicity for man. The antiChE compound most widely used at the present time is parathion (p-nitrophenyl diethyl thionophosphate).<sup>1</sup> This anticholinesterase was introduced by the Germans and is now manufactured in this country, chiefly for use as an insecticide in agriculture, under such names as "Geigy Parathion," "Lethalaire G-54 Parathion Aerosol," "Chipman Parathion," "P. A. R. Parathion," "Phos Kit Parathion," "Paradust Parathion," "Dow Parathion," "Vapophos Parathion," "Penphos Parathion," "Aphamite Parathion," "Parathion Insecticides," "Genithion Parathion," "Edco 15 Parathion," and "Niran (Parathion)." Studies performed following the administration of parathion to experimental animals have shown that most of the pharmacological properties of this compound can be explained in terms of its antiChE action.<sup>2,3</sup>

Detailed studies of the effects in man of other esters of phosphoric and pyrophosphoric acid which are potent antiChE agents, such as di-isopropyl fluorophosphate (DFP) and tetraethyl pyrophosphate (TEPP, which is also employed as an insecticide), have shown that these esters produce muscarine-like, nicotine-like, and central nervous system effects.<sup>4-8</sup> Because the inhibition of cholinesterase (ChE) enzymes by DFP is irreversible, and by TEPP and parathion only partly reversible, the effects of these compounds are prolonged and cumulative. Until the ChE enzymes of the tissues have been restored, subjects who have been exposed to these compounds remain susceptible to the effects of any subsequent exposure, which may be by any route, including absorption from the skin, respiratory tract, conjunctivae, gastrointestinal tract, or following injection.

The following case report is that of a man who died after repeated exposure to the insecticide, parathion, and who manifested the characteristic cholinergic symptoms and changes in ChE activity attributable to an antiChE agent.

### CASE REPORT

A. N., a white male aged 35, was employed as a mixer of liquid parathion (97 per cent pure) and ataclay (a clay powder) to produce a clay dust with parathion

\* Received for publication August 16, 1949.

Work was performed in part under a contract between the Medical Division, Chemical Corps, U. S. Army, and the Johns Hopkins University.

From the Department of Medicine, Johns Hopkins University and Hospital, the Department of Surgery, Mercy Hospital, and the Office of the Chief Medical Examiner, Baltimore, Maryland.

The patient was treated with atropine sulfate, 0.6 mg. being injected intramuscularly four times during the first hour. This resulted in diminution of the excessive sweating, salivation, and bronchial secretion. Two hours later he received another injection of 0.6 mg. atropine sulfate. He was given a continuous infusion of saline and glucose. During his first convulsion he was given 140 units of curare intravenously over a period of three minutes. This diminished the severity of the convulsive movements, but did not prevent their recurrence. The curare immediately abolished the muscular fasciculations. He was given a second injection of curare (100 units) about half an hour after the first injection.

The patient remained comatose and areflexic for four hours. Then, seven hours after the onset of symptoms, he began to respond again to painful stimuli, and tendon reflexes could again be elicited. The pupils became less pin-point, and some response to light was obtained. Coincident with this improvement the blood pressure gradually fell from 186/100 to 150/80. One hour after the return of reflexes and of response to painful stimuli the patient regained consciousness, spoke a few words and appeared to be rational and oriented. He stated that vision in both eyes was blurred, and that he had difficulty focussing. During the next two hours he appeared to be improving gradually, becoming more alert and speaking more easily. However, shortly thereafter, 10 hours after the onset of symptoms, respiration became shallow, rapid, and labored, and the pulse unobtainable. Fifteen minutes after this change was noted the patient died.

#### AUTOPSY FINDINGS

Postmortem examination, performed four hours after death, revealed only diffuse vascular engorgement throughout the body, with widespread capillary dilatation, edema, and hyperemia of all the organs, including the lungs, liver, spleen, kidneys, and brain. The brain was edematous, and there was an increased amount of clear cerebrospinal fluid in the ventricles and subarachnoid space, as well as a "pressure cone." There was a slightly increased amount of mucus in the trachea and bronchi. These findings are in general similar to those that were observed after a death attributable to neostigmine methylsulfate.<sup>9</sup>

TABLE I

Comparison between the ChE activity of various tissues of patient A. N., and the average activity of four subjects who had received no exposure to any anticholinesterase agent and who were autopsied a similar length of time after death due to other causes. The ChE activity is expressed in millimoles of acetylcholine bromide hydrolyzed per minute per gram of tissue per ml. Determinations were made manometrically.<sup>4</sup>

	Cholinesterase Activity		
	Control Average	A. N.	A. N.
	mM ACh Br $\times 10^{-3}$		% of Control Average
Plasma	9.9	0.5	5
Red blood cells	14.0	1.7	12
Liver	3.5	1.5	43
Kidney	2.2	0.9	41
Cerebral cortex	4.8	0.6	12
Thalamus	34.0	12.3	36
Cerebellum	13.1	6.2	47
Pons	7.5	2.4	32
Medulla	3.6	1.2	30

Following the occurrence of this death due to exposure to parathion, employees at the chemical company in which the death occurred have received periodic determinations of plasma and red blood cell ChE activity, in order to detect those employees who have absorbed this compound.<sup>12</sup> Employees with reduced ChE activity of the plasma or red blood cells have been removed from all exposure to parathion until the ChE activity returned to normal, over a period of several weeks. It is strongly urged that this procedure, as well as all possible safety measures to reduce the degree of exposure and of absorption, be used in any installation or situation in which there is exposure to an antiChE compound, whether in the production, packaging, handling, or spraying of these compounds, in the harvesting of fruits or vegetables on which they have been sprayed, or in their ingestion on insufficiently weathered fruits or vegetables.

The treatment of the effects of excessive exposure or overdose of antiChE compounds relies chiefly on atropine. This may be administered in very large doses in such a situation, as high as 2 to 3 mg. intramuscularly every hour as long as cholinergic symptoms are present, since the tolerance for atropine is greatly increased by the action of the antiChE compound.<sup>8</sup> It is probable that the patient described above should have received larger amounts of atropine than were administered. Other therapeutic measures include washing the skin and gastric lavage to remove any unabsorbed antiChE compound, parenteral replacement of fluids, and administration of oxygen. If muscular weakness is marked and involves the muscles of respiration, intubation and mechanical aid to respiration may become necessary. The administration of curare results in the cessation of muscular fasciculations, but since an overdose may cause weakness of the muscles of respiration, its use is probably not advisable.

#### SUMMARY

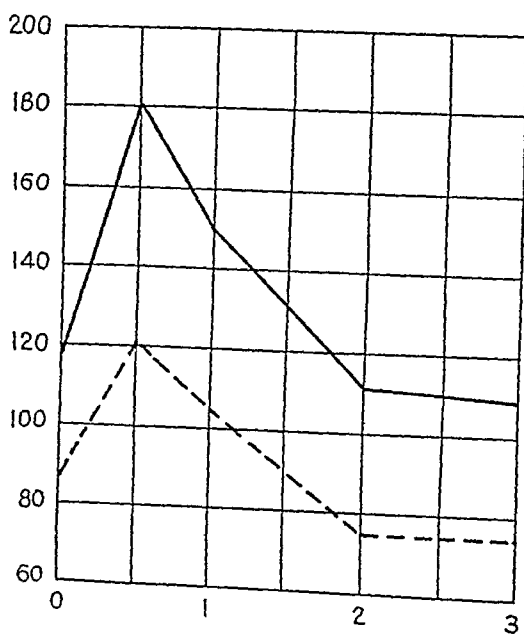
A report has been presented of a man who died following repeated exposure to the antiChE insecticide, parathion. Safety measures to reduce exposure and absorption, and periodic determinations of plasma and red blood cell ChE activity, are strongly recommended for all persons exposed to this, or any related, antiChE compound.

#### BIBLIOGRAPHY

1. HALLER, H. L.: Chemical aspects of some of the newer insecticides, *Bull. N. Y. Acad. Med.*, 1949, xxv, 374-381.
2. DuBOIS, K. P., DOULL, J., SALERNO, P. R., and COON, J. M.: Studies on the toxicity and mechanism of action of parathion, *Jr. Pharmacol. and Exper. Therap.*, 1949, lxxxv, 79-91.
3. LEHMAN, A. J.: The major toxic actions of insecticides, *Bull. N. Y. Acad. Med.*, 1949, xxv, 382-396.
4. GROB, D., LILIENTHAL, J. L., JR., HARVEY, A. M., and JONES, B. F.: The administration of di-isopropyl fluorophosphate (DFP) to man. I. Effect on plasma and erythrocyte cholinesterase; general systemic effects, use in study of hepatic function and erythropoiesis; and some properties of plasma cholinesterase, *Bull. Johns Hopkins Hosp.*, 1947, lxxxi, 217-244.
5. GROB, D., LILIENTHAL, J. L., JR., and HARVEY, A. M.: The administration of di-isopropyl fluorophosphate (DFP) to man. II. Effect on intestinal motility and use in the treatment of abdominal distention, *Bull. Johns Hopkins Hosp.*, 1947, lxxxi, 245-256.

strated varying incidence of hepatic dysfunction in patients with Graves' disease. In those tests involving the metabolism of carbohydrates (glucose and galactose tolerance tests) <sup>25, 26, 28</sup> the authors pointed out that the abnormal results may be a reflection of multiple derangements of carbohydrate absorption and metabolism in thyrotoxicosis of which impaired hepatic handling is only a part. Therefore these tests may not be a true indication of the severity of hepatic involvement per se.

In addition to these clinical studies there have been parallel investigations of autopsy material in large series of patients who died with Graves' disease, excluding those with known independent hepatic disease.<sup>5, 15, 17, 20, 41-48</sup> With but one exception,<sup>48</sup> these authors have all described a variety of acute and chronic changes, occurring with remarkable consistency, over and beyond the changes of chronic passive congestion secondary to thyrotoxic heart disease. According to



GRAPH 1. Glucose tolerance tests (100 gm. glucose).

Beaver and Pemberton<sup>5</sup> the more acute lesions (fatty changes, central and focal necrosis) have been directly proportional to the severity of the thyrotoxicosis as measured by the basal metabolic rate while the more chronic lesions (atrophy and cirrhosis) have been more related to the duration of the disease.

Duplicating all these clinical studies have been a great many experimental studies in a wide variety of animals, largely rats and dogs but also cats, rabbits, guinea pigs and dormice. Experimental hyperthyroidism has been induced by the feeding of desiccated thyroid gland. The results have been in line with the findings in clinical cases of thyrotoxicosis. Pathological evidence of liver damage was demonstrated <sup>29, 49, 50</sup>; function studies with the use of bromsulfalein retention <sup>51, 52</sup> and IV galactose tolerance tests <sup>29</sup> have shown impairment; marked glycogen depletion of the liver and impaired glycogenesis have been demonstrated <sup>53-56</sup>; and both relative and absolute hypertrophy of the liver and spleen

## CASE REPORT

A 19 year-old male, in previous excellent health, was admitted on October 3, 1946 with a six to nine month history of nervousness, tremors, weakness, increased appetite, increased sweating, shortness of breath on exertion, evening ankle edema, and slight enlargement of the size of his neck. Initial physical examination revealed: a bilaterally palpable, slightly enlarged thyroid gland, without nodules; a warm moist skin, a slight stare, blood pressure of 145 mm. Hg systolic and 60 mm. diastolic, pulse rate of 108, an apical systolic murmur, a coarse tremor of the extended hands, and palpable liver and spleen each extending about two fingers' breadth below the costal margin. Impression on admission was thyrotoxicosis with hepatosplenomegaly, possibly due to liver damage secondary to Graves' disease.

Initial work-up included the following: basal metabolic rate (average of six calculations) +41; blood cholesterol (average of two) 119 mg. per cent; circulation time (average of two) 8.5 sec.; \* normal blood counts except for a marked lympho-

TABLE I  
Comparison of Tests of Thyroid and Hepatic Function

	On Admission	3 Mos. Postop.
1. Pulse pressure	85	40
2. Pulse rate	108	88
3. Circ. time (calcium gluconate)*	8.5 sec.	15 sec.
4. BMR*	+41	+3
5. Bl cholesterol	119	247
6. Lymphocyte percentage* in blood	67%	47%
7. Liver size	2 F B ↘	2 F B ↘
8. Spleen size	2 F B ↘	barely palpable
9. BSP retention* (5 mg./kilo)	35%	7.5%
10. Oral hippuric test	1.39 G	2.9 G
11. Glucose tolerance curve (see graph)	abnormal	normal
12. Icterus index	7	9
13. Urine for bile and increased urobilinogen	negative	negative
14. Total protein	6.8	7.6
Albumin	5.3	4.4
Globulin	1.5	3.2
15. Prothrombin index	normal	normal

\* Figures refer to average of several determinations.

cytosis of the peripheral blood of (average of three) 66 per cent. It was felt that the above findings of elevated basal metabolic rate, lowered blood cholesterol, decreased circulation time, and lymphocytosis of peripheral blood all fitted with and confirmed the clinical impression of thyrotoxicosis. Electrocardiogram was normal and chest roentgen-ray was normal with no evidence of substernal thyroid.

Because of the hepatosplenomegaly, the hepatic function was investigated. Bromsulfalein retention at 30 min. with 5 mg./kilo was 35 per cent; oral hippuric test revealed excretion of 1.39 gm. benzoic acid; glucose tolerance curve showed 118 mg. per cent fasting level; 180 at one-half hr.; 150 at one hour; 112 at two hours; 109 at three hours. Icterus index 7; total protein 6.8 gm. per cent with 5.3 gm. albumin and 1.5 gm. globulin. The urine was negative for bile and for increased urobilinogen; prothrombin index normal. Though some of these tests were normal, the more sensitive ones, bromsulfalein and oral hippuric, revealed a considerable degree of hepatic

\* 3 c.c. calcium gluconate intravenously: arm to tongue time.

ated elevated basal metabolic rate so often seen in leukemic patients. The absence of lymphadenopathy, of immature white cells in the peripheral blood and of anemia served to exclude this possibility. The reversal of the peripheral blood picture and of the splenomegaly after thyroidectomy was further evidence against the diagnosis of leukemia. The absence of increased red cell fragility, of spherocytes on blood smear, of signs of increased hemolysis, and of reticulocytosis served readily to differentiate familial hemolytic icterus. The patient had never been in a malarious area, had no history of fever and chills, and repeated smears after adrenalin were negative for malaria.

That the liver damage and hepatomegaly were not part of an independent cirrhosis of the liver was established by the reversal of the picture subsequent to thyroidectomy. There was incidentally no history of alcoholism or dietary deficiency of any type. The absence of icterus, of gastrointestinal symptoms, especially anorexia and nausea, and of the signs of acute illness ruled out a concomitant but unrelated acute infectious hepatitis. We were therefore left with the conclusion, amply supported by the evidence cited from the literature, that we were dealing with a case of liver damage secondary to thyrotoxicosis and that in this case the liver damage extended to the admittedly more rare presence of definite hepatosplenomegaly. This case is being reported largely to call attention to the fact that hepatosplenomegaly occurring in conjunction with Graves' disease can be part of the clinical picture and that it together with the chemical evidences of hepatic dysfunction can be expected to reverse itself when the underlying thyrotoxicosis is adequately treated.

The obvious corollary is that a careful evaluation of the hepatic function should be part of the work-up of every thyrotoxic patient, especially those in whom surgery is contemplated. The importance of this preoperative evaluation and the preoperative fortification of the damaged liver is stressed by numerous writers on this subject.<sup>20, 21, 24, 66, 68, 70, 71</sup> Of 250 patients with thyrotoxicosis seen in Schmidt's clinic, 60 per cent had a definite impairment of liver function on the basis of the oral hippuric acid test.<sup>24</sup> The magnitude of this relationship needs constant reëmphasis.

### SUMMARY

A case of relatively mild thyrotoxicosis with marked liver damage and secondary hepatosplenomegaly is presented. Attention is called to the fact that the liver damage so often found in patients with Graves' disease can be severe enough to cause definite enlargement of the liver and spleen and that these findings though unusual are not incompatible with the clinical picture of thyrotoxicosis. The hepatic dysfunction was reversed by subtotal thyroidectomy.

### BIBLIOGRAPHY

1. PAUL, quoted by SHAFFER, J. M.<sup>18</sup>
2. ACREE, F. M.: Graves' disease complicated by acute catarrhal jaundice; case report, *Trans. Am. Assoc. Goiter*, 1939, 50-52.
3. BARR, J. S., and LOURIA, H. W.: Jaundice associated with toxic goiter, *Am. Jr. Surg.*, 1936, xxxiv, 338.
4. BARKER, L. F.: Thyreo-intoxication with necrosis and atrophy of the liver, damage to the heart muscle and kidneys and terminal broncho-pneumonia, *Med. Clin. N. Am.*, 1930, xiv, 261-263.



33. BARTELS, E. C.: Serum protein studies in hyperthyroidism, *New Eng. Jr. Med.*, 1938, CCXVIII, 289-294.
34. HURXTHAL, L. M.: Blood cholesterol in thyroid disease. II. Effect of treatment, *Arch. Int. Med.*, 1933, lii, 86-95.
35. SANGER, B. J., and HUN, E. G.: Glucose mobilization rate in hyperthyroidism, *Arch. Int. Med.*, 1922, xxx, 397-406.
36. RAGINS, A. B.: The value of the Takata and Ara reaction as a diagnostic and prognostic aid in cirrhosis of the liver, *Jr. Lab. and Clin. Med.*, 1935, xx, 902-913.
37. YOUNG, J. B., and WARFIELD, L. M.: Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency, *Arch. Int. Med.*, 1926, xxxvii, 1-17.
38. LICHTMAN, S. S.: Liver function in hyperthyroidism, *Arch. Int. Med.*, 1932, i, 721-729.
39. BARTLETT, W., JR.: Role of the liver in thyrotoxicosis, *Surgery*, 1938, iii, 261-262.
40. SNAPPER, I., and SALTZMAN, A.: Excretion of benzoyl glucuronate as a test of liver function, *Am. Jr. Med.*, 1947, ii, 334-341.
41. CAMERON, G. R., and KARUNARATNE, W. A. E.: Liver changes in exophthalmic goiter, *Jr. Path. and Bact.*, 1935, xli, 267-282.
42. HABÁN, G.: Über die Leberveränderungen bei Morbes Basedowii mit besonderer Berücksichtigung der Lebercirrhose, *Beitr. path. Anat.*, 1933-34, xcii, 88-100.
43. LEWIS, W.: Hyperthyroidism and associated pathology, *Am. Jr. Med. Sci.*, 1931, clxxxi, 65-74.
44. MARINE, D., and LENHART, C. H.: Pathological anatomy of exophthalmic goiter, *Arch. Int. Med.*, 1911, viii, 265-316.
45. MOSCHCOWITZ, E.: Pathogenesis of cirrhosis of the liver occurring in patients with diffuse toxic goiter, *Arch. Int. Med.*, 1946, lxxviii, 497-530.
46. RÖSSE, R.: Über die Veränderungen der Leber bei der Basedowschen Krankheit und ihre Bedeutung für die Entstehung anderer Organsklerosen, *Virchow's Arch.*, 1933, CCXCI, 1-46.
47. WELLER, C. V.: Hepatic lesions associated with exophthalmic goiter, *Trans. Assoc. Am. Phys.*, 1930, xlv, 71-76.
48. WELLER, C. V.: Hepatic pathology in exophthalmic goiter, *Ann. Int. Med.*, 1933, vii, 543-560.
49. FARRANT, R.: Hyperthyroidism, its experimental production in animals, *Brit. Med. Jr.*, 1913, ii, 1363-1367.
50. HASHIMOTO, H.: The heart in experimental hyperthyroidism with special reference to its histology, *Endocrinology*, 1921, v, 579-606.
51. DRILL, V. A., and HAYS, H. W.: Studies on the relation of the liver function, pulse rate, and temperature of hyperthyroid dogs to vitamin B<sub>1</sub> and yeast, *Am. Jr. Physiol.*, 1942, CXXXVI, 762-771.
52. DRILL, V. A., SHAFFER, C. B., and OVERMAN, RICHARD: Liver function, pulse rate and temperature of hyperthyroid dogs. Effects of a yeast-free diet and a high B vitamin diet, *Am. Jr. Physiol.*, 1943, CXXXVIII, 370-377.
53. BUELL, M. V., and STRAUSS, M. B.: Liver function in experimental hyperthyroidism, *Jr. Biol. Chem.*, 1934, xiv, 105.
54. COGGESHALL, H. C., and GREENE, J. A.: The influence of desiccated thyroid gland, thyroxin, and inorganic iodine, upon the storage of glycogen in the liver of the albino rat under controlled conditions, *Am. Jr. Physiol.*, 1933, cv, 103-109.
55. DRILL, V. A.: The effect of yeast on the liver glycogen of white rats during hyperthyroidism, *Jr. Nutr.*, 1937, xiv, 355-363.
56. FRAZIER, C. H., and FRIEMAN, H.: Alterations in liver glycogen following thyroid, iodine, and glucose feedings, *Surg., Gynec. and Obst.*, 1935, lx, 27-29.
57. HEWITT, J. A.: The effect of administration of small amounts of thyroid gland on the size and weight of certain organs in the male white rat, *Quart. Jr. Exper. Physiol.*, 1919-20, xii, 347-354.

in a patient with hypertensive and coronary heart disease by the use of all the measures which are available to the physician of today.

### CASE REPORT

A 61 year old physician was first seen in August, 1945, because of shortness of breath and dependent edema. The patient had always enjoyed good health, although he had been somewhat nervous all of his life. Seven years previously his blood pressure had been found to be elevated, the systolic level ranging from 180 to 200 millimeters of mercury. One year previously, in July, 1944, the patient was taken in the street with severe left anterior chest pain with radiation to the left arm. The pain lasted for 45 minutes, being relieved at that time by morphine. The following day, while he was at home in bed, the pain recurred and lasted one hour, again requiring morphine for relief. The patient was seen at this time by a competent cardiologist, and after reviewing the electrocardiograms he felt that the patient was suffering from coronary insufficiency but did not believe that a myocardial infarction had occurred. The patient was in bed four weeks and about the house for another month, after which time he returned to work.

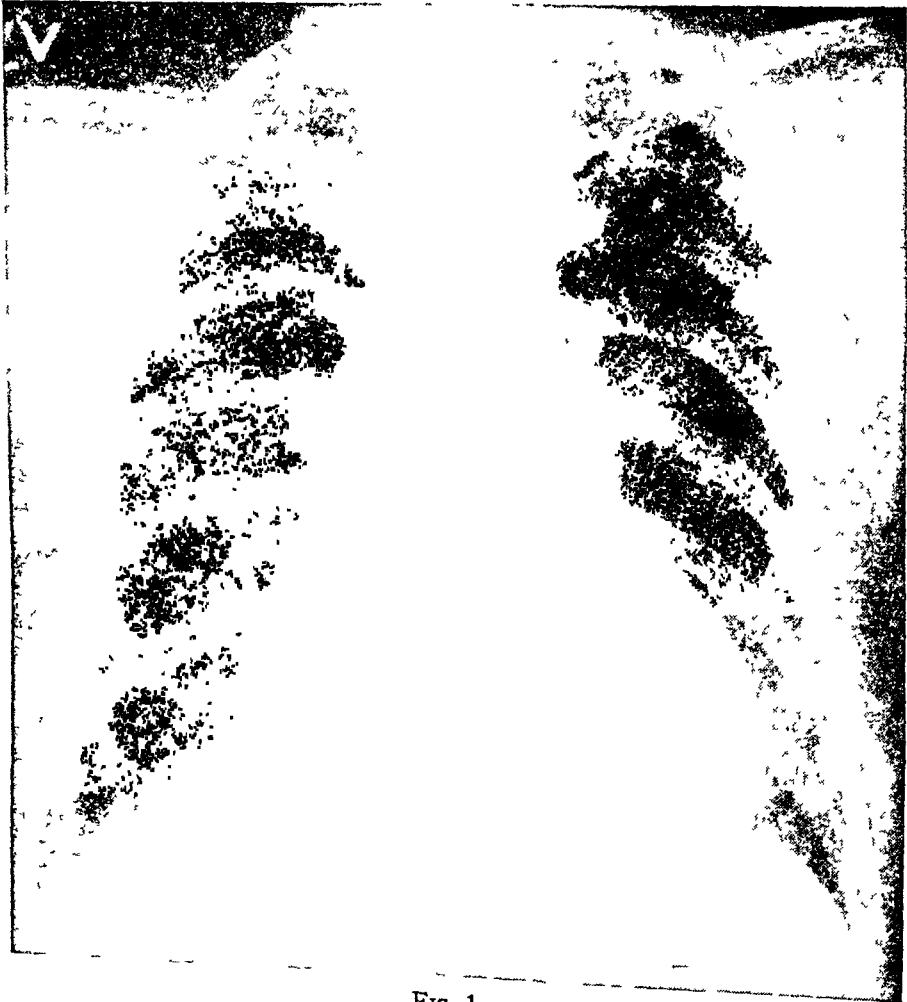


FIG. 1.

A. Teleroentgenogram of the chest on July 25, 1945, demonstrating a large heart measuring 19.6 centimeters in diameter.

## CASE REPORTS

The patient's revised treatment consisted of increasing the dosage of ammonium chloride from 3 grams to 6 grams per day and of digitalis to 0.2 gram each day for 10 days and mercurial diuresis (2 c.c. of Mercupurin) on three occasions. He was also placed upon a low sodium dietary regime. The diet contained about 0.5 gram of sodium per day with a neutral ash content. The fluids were increased from about 1400 c.c. a day to around 2000 c.c. a day. In the course of the next few weeks

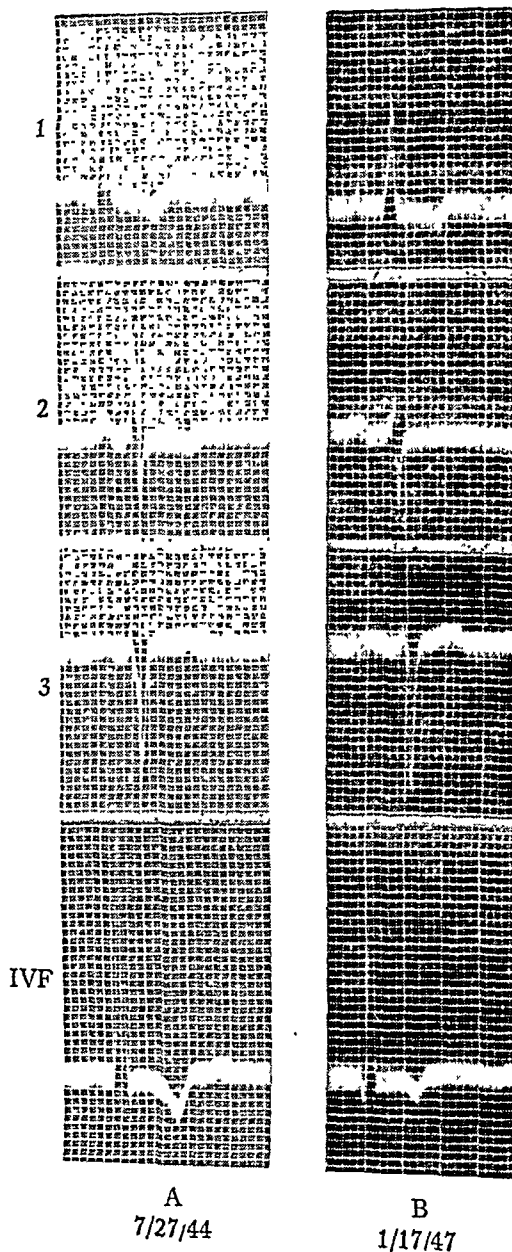


FIG. 2.

A. The electrocardiogram taken in July, 1944, several days after the patient had severe chest pain on two successive days. The pattern is quite characteristic of left ventricular strain and hypertrophy with or without the presence of coronary heart disease.

B. Repeat electrocardiogram of January, 1947, reveals little change, although the T waves in Leads I and IV are somewhat less negative and the R waves in Leads I and II are shorter. There has been surprisingly little variation in the tracings from July, 1944, to January, 1947.

It is interesting to note that in spite of this remarkable reduction in heart size there was no commensurate improvement of the electrocardiogram, although there was a slight return toward the normal (figure 2). This is possibly accounted for by the presence of coronary heart disease with very likely some scarring of the myocardium. The continued hypertension may also be an important factor in the persistent electrocardiographic pattern. The change in the blood pressure was not remarkable in spite of the low sodium intake over a prolonged period of time. Other diets have been reported to be of value in the treatment of cardiac dropsy, the salient feature of which undoubtedly is the low sodium content.<sup>4, 6, 7</sup> An additional item of some importance in the course of this man's recovery may have been a subsidence of activity of coronary heart disease through the spontaneous development of collateral circulation which is of such common occurrence in the evolution of disease of the coronary arteries.

### SUMMARY

Remarkable decrease in heart size is reported in the case of a man aged 61 years treated for severe congestive heart failure secondary to hypertension and coronary arterial disease. The therapy included adequate digitalization, the use of ammonium chloride and mercurial diuretic, and a sharp restriction of sodium intake. The sodium restriction was in large measure doubtless responsible for the two years of good health that followed.

We wish to acknowledge the coöperation of Dr. Roberto Zachrisson, Guatemala City in the case of this patient.

### BIBLIOGRAPHY

1. SCHROEDER, H. A.: Studies in congestive heart failure, *Am. Heart Jr.*, 1941, xxii, 141.
2. PROGER, S., GINSBURG, E., and MAGENDANTZ, H.: Effects of ingestion of excessive amounts of sodium chloride and water on patients with heart disease, *Am. Heart Jr.*, 1942, xxiii, 555.
3. ELLIS, L. B.: Relative importance of salt and fluid in the management of congestive heart failure, *Trans. New Eng. Heart Assoc.*, 1942, 33-34.
4. SCHEMM, F. R.: High fluid intake in management of edema, especially cardiac edema. I. Details and bases of regime, *Ann. Int. Med.*, 1942, xvii, 952; High fluid intake in management of edema, especially cardiac edema. II. Clinical observations and data, *Ann. Int. Med.*, 1944, xxi, 937.
5. WHEELER, E. O., BRIDGES, W. C., and WHITE, P. D.: Diet low in salt (sodium) in congestive heart failure, *Jr. Am. Med. Assoc.*, 1947, xvi, 133.
6. KEMPNER, WALTER: Treatment of cardiac failure with the rice diet, *North Carolina Med. Jr.*, 1947, viii, 128.
7. KARRELL, P.: De le cure de lait, *Arch. gén. de méd.*, 1866, ii, 513.

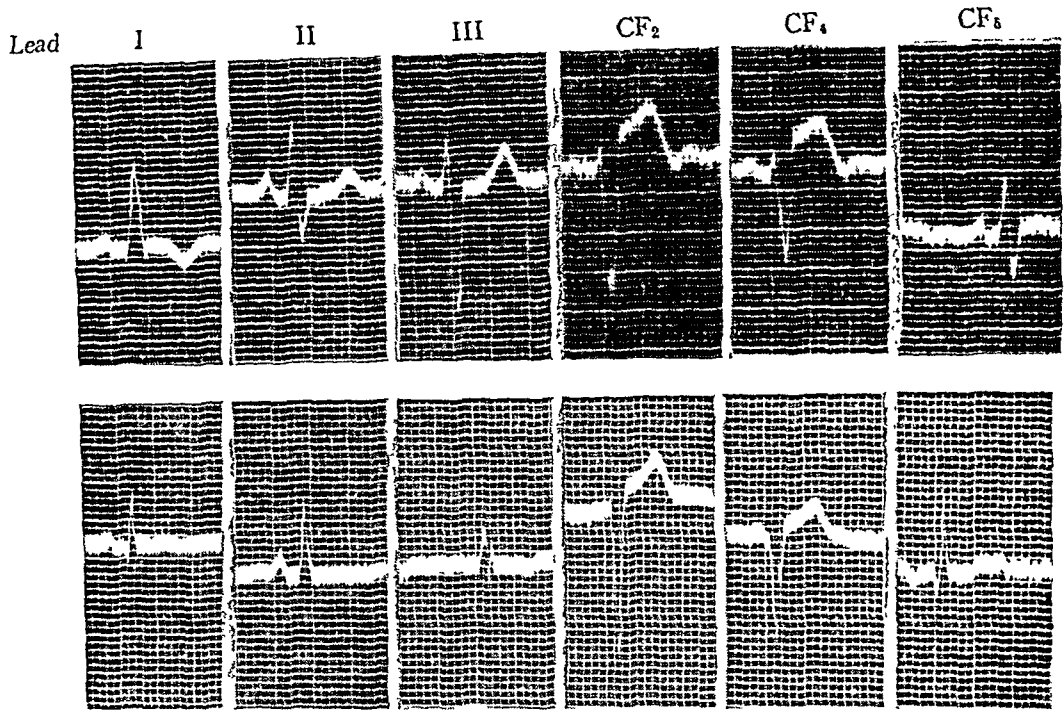


FIG. 1 A. (above) October 4, 1946. Day following admission to hospital.

FIG. 1 B. (below) October 7, 1946. Three days after admission to hospital.

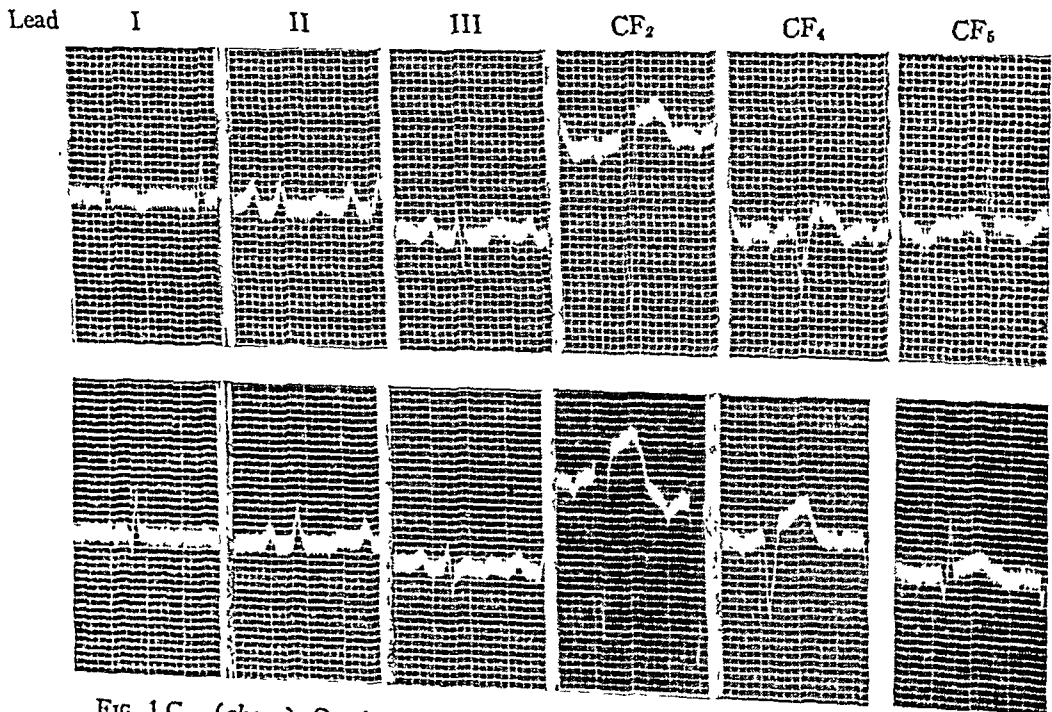


FIG. 1 C. (above) October 14, 1946. Ten days after admission, and six hours after septal perforation.

FIG. 1 D. (below) October 16, 1946. Twelve days after admission; two days after septal perforation, and four days prior to death.

the patient developed slight dyspnea and non-productive cough. Heart tones were distant; no murmurs were audible. The patient was considered to have developed pulmonary edema incident to left ventricular failure due to recent severe myocardial infarction. Morphine and oxygen were effective in relieving the respiratory distress.

At 7:30 a.m. on October 14, the patient complained of nausea and pain in a rather localized area on the lateral surface of the middle one-third of the left arm.



FIG. 3. Right ventricular view of the septal perforation.

Generalized, severe, intimal hyalinization was found in the arterioles throughout the viscera. In the kidneys this was accompanied by arterial and arteriolar nephrosclerosis as manifested by a firmly adherent renal capsule, cortical scarring, glomerular hyalinization, and tubular atrophy. Atrophy of a portion of the left renal cortex had resulted from compression by a cyst found in the capsule of this kidney. This cyst measured 5 cm. in diameter and was filled with uncoagulated, semi-solid, dark brown blood.

The other findings are listed below, together with those mentioned in the foregoing paragraphs, and were non-contributory to the clinical course of the patient.

The complete pathologic diagnoses in this case were:

Arteriosclerosis, generalized, severe, with calcification and ulceration. Thrombus, occlusive, in left coronary artery, anterior descending branch, 2 cm. distal to bifurcation. Infarct, acute, of myocardium of left ventricle, anterior wall, and of interventricular septum, apical. Perforation of interventricular septum, secondary to infarction. Thrombus, mural, left ventricular, of septal and lateral walls, adherent, organizing. Patency of foramen ovale, with apposition of primary and secondary septa. Atheromatosis of aortic and mitral valves, moderate. Edema, pulmonary, acute, bilateral, severe. Pneumonia, lobar, acute, right lower lobe. Necrosis, central, acute, congestive, of liver, with mild fatty degeneration. Edema, subcutaneous, of dorsa of feet, mild. Arteriosclerosis, severe, of spleen, pancreas, kidneys, adrenals, thyroid. Nephrosclerosis, arterial and arteriolar, moderate, bilateral. Degeneration, hyalin, of collagen, of renal pyramids. Cyst of renal capsule, left, with hemosiderosis. Atrophy of kidney, left, local, compression. Edema of intima of descending aorta. Infarcts of spleen, anemic, acute, multiple, subcapsular, with associated venous thrombosis and arteritis, acute. Perisplenitis, acute, mild. Hyaline deposits in spleen, corpuscular. Infarct, pulmonary, healed, peripheral, right middle lobe, small. Emphysema, marginal, of left lung, mild. Anthracosis, pulmonary, bilateral, mild. Atrophy, senile, of uterus, Fallopian tubes and ovaries. Cysts, Nabothian, of endocervical canal. Fibrosis of appendix, obliterative. Adhesions, fibrous, peritoneal, between parietal peritoneum and ileum, splenic flexure of colon, sigmoid colon, and between spleen and descending colon. Adhesions, fibrous, pleural, anterior, apical, of left lung. Hydrothorax, left, moderate (250 c.c.). Lipoma, subcutaneous, of left antecubital fossa.

#### COMMENT

The diagnosis of this condition should not be difficult if the possibility is kept in mind, in a patient with a known coronary thrombosis and myocardial infarction, the sudden development of a systolic murmur located over or slightly to the left of the lower portion of the sternum at the fourth and fifth intercostal space is highly suggestive of septal perforation. Myocardial infarction with rupture of a papillary muscle might conceivably cause confusion, although in this the murmurs are reported as more bizarre, less well localized and may be associated with considerable cardiac enlargement.<sup>1</sup> Left ventricular dilatation with systolic murmur is likely to develop more slowly.

The general appearance and condition of the patient were the same as ordinarily seen in infarction without perforation, and death occurred from the severity of the infarction rather than from the fact that the septum incidentally perforated in the process. The average length of life in 10 patients following septal perforation is reported to be between nine hours and seven days, with an average of 2.25 days (Edmondson and Hoxie<sup>3</sup>), although Wood and Livezey<sup>4</sup> report a case of a man 44 years of age who survived five years following septal perforation, ultimately dying in congestive failure.

## EDITORIAL

### *SOME ASPECTS OF ADRENAL CORTICAL FUNCTION AND PITUITARY-ADRENAL RELATIONSHIPS*

IN April, 1949 Hensch et al.<sup>1</sup> reported that the administration of one of the adrenal cortical hormones, 17-hydroxy-11-dehydrocorticosterone (Compound E), produced beneficial effects of a striking nature in a group of patients with advanced rheumatoid arthritis. Withdrawal of the hormone was followed by the recurrence of signs and symptoms of the disease. Essentially similar results were obtained in several patients who were given adrenocorticotrophic hormone (ACTH) derived from hog pituitary. In a subsequent paper<sup>2</sup> these investigators reported that the administration of compound E to three patients with acute rheumatic fever was also followed by rapid subsidence of clinical evidences of the disease. These findings have recently been confirmed by Thorn et al.<sup>3</sup> who have, in addition, reported preliminary observations indicating a beneficial response in several patients with acute disseminated lupus erythematosus and gouty arthritis. Unpublished observations indicate that similar responses have occurred in several disease entities of allergic etiology.

In all these reports, the fact has been stressed that the observations were to be considered as of a preliminary nature. The periods of study have been relatively short. The possible toxic effects of long term administration of these agents have yet to be evaluated. Furthermore, the scarcity and expense of the hormones have precluded widespread and prolonged use. Nevertheless, these reports have not only aroused great interest but have resulted in considerable speculation regarding the mode of action of the agents. They have succeeded also in challenging certain time-honored, even though inadequate, concepts of the pathogenesis of these diseases. Although it is impossible at this time to provide a complete pharmacologic rationale for the action of these hormones, it may, nevertheless, be profitable to examine some of the known metabolic effects of the adrenal cortical steroid hormones as well as some aspects of the pituitary-adrenal relationship.

In a recent report Gaunt and Eversole<sup>4</sup> have provided a brief, but excellent perspective of the entire adrenal cortical problem. Stewart<sup>5</sup> stated

<sup>1</sup> HENCH, P. E., KENDALL, E. C., SLOCUMB, C. H., and POLLEY, H. F.: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis; preliminary report, Proc. Staff Meet. Mayo Clinic, 1949, xxiv, 181.

<sup>2</sup> HENCH, P. E., SLOCUMB, C. H., BARNES, A. R., SMITH, H. L., POLLEY, H. F., and KENDALL, E. C.: The effects of the adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (compound E) on the acute phase of rheumatic fever: preliminary report, Proc. Staff Meet. Mayo Clinic, 1949, xxiv, 277.

<sup>3</sup> THORN, G. W., BAYLES, T. B., MASSELL, B. F., FORSHAM, P. H., HILL, S. R., SMITH, S., and WARREN, J. E.: Studies on the relation of pituitary-adrenal function to rheumatic disease, N. Eng. Jr. Med., 1949, ccxli, 529.

<sup>4</sup> GAUNT, R., and EVERSOLE, W. J.: Notes on the history of the adrenal cortical problem, Ann. N. Y. Acad. Sci., 1949, i, 511.

<sup>5</sup> STEWART, G. N.: Adrenalectomy and the relation of the adrenal body to metabolism, Physiol. Rev., 1924, iv, 163.



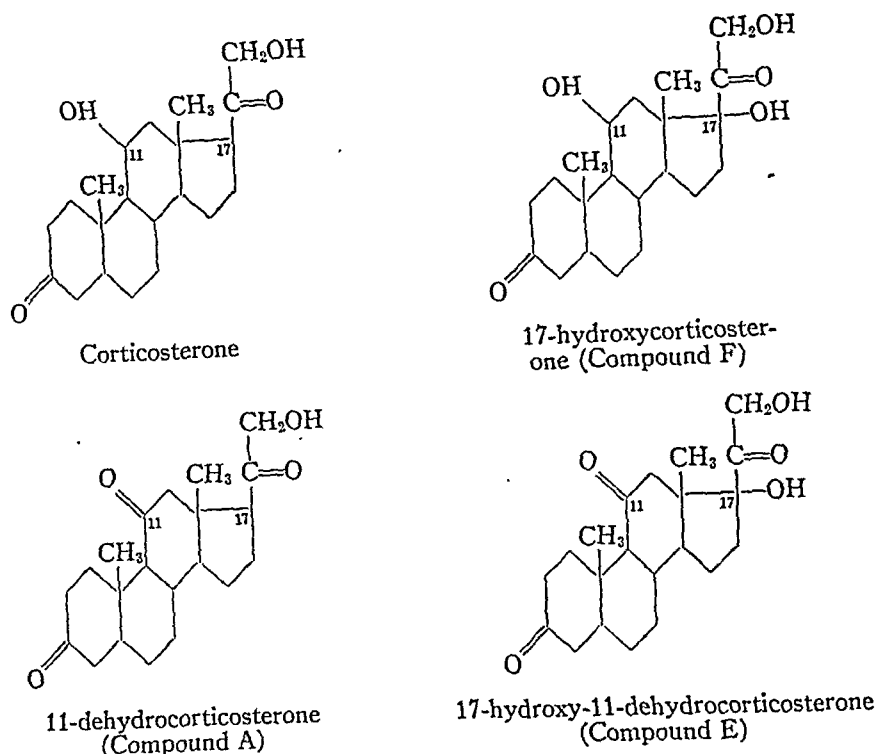


FIG. 2

The corticosteroids oxygenated at Carbon 11. These have a predominant effect on organic metabolism.

It is now known that the adrenal cortical steroids fall into three groups with reference to their physiological activity, namely, those which have a predominant effect on electrolyte and fluid balance, those which are concerned primarily with the intermediary metabolism of protein and carbohydrate, and those which have an androgenic and anabolic effect.<sup>10</sup> Any attempt to provide a concise summary of the rôle played by these steroids in physiological processes involves a great risk of oversimplification. Furthermore, it should be pointed out that there is experimental evidence of overlapping of functions between these groups. The lack of exact knowledge of the metabolic functions of the amorphous fraction leaves an unavoidable gap in any presentation of the subject at this time. With these limitations in mind a brief summary of the available information can be attempted.

For greater clarity of understanding the structural formulae of the six steroids which possess biological activity are presented (figures 1 and 2). It will be observed that the major difference between the two groups consists in the absence of an oxygen molecule (desoxy-) at Carbon 11 in the first group and its presence, in either keto- or hydroxy form, at Carbon 11 in the second group. The first group are known collectively, as desoxycorticosterones, while the latter are referred to as corticosterones. The adrenal

<sup>10</sup> SWINGLE, W. W., and REMINGTON, J. W.: The rôle of the adrenal cortex in physiological processes, *Physiol. Rev.*, 1944, xxiv, 89.

lation, in impure form, of adrenocorticotrophic hormone. However, it was not until 1943 that a pure form of the hormone, unadulterated by other secretions of the gland, was obtained by several groups of investigators.<sup>14, 15</sup> Since that time it has become possible, with greater precision, to study pituitary-adrenal relationships. In a manner common to other glandular interrelationships, there is apparently an internal self-regulatory mechanism between the adrenal cortex and the anterior pituitary. Increased concentration of corticosteroids in the circulating blood has an inhibitory effect upon the secretion of ACTH while a diminished quantity of the adrenal hormones results in antithetical activity.

The administration of ACTH is followed by striking morphological and biochemical changes in the adrenals of several animal species.<sup>16</sup> The biochemical changes largely concern the concentration of cholesterol and ascorbic acid. The adrenals contain a high concentration of cholesterol which is in a labile state. The administration of a single dose of ACTH results, within 3 hours, in a 50 per cent drop in the concentration of cholesterol in the gland. By the end of 24 hours the concentration of this substance has returned to normal. During the period of cholesterol depletion evidences of increased cortical hormone activity may be observed. Although no direct evidence exists as yet it is believed that the cholesterol is utilized in the formation of steroid hormones. Simultaneous depletion of the ascorbic acid content of the adrenal occurs after ACTH administration. This substance likewise reaccumulates to a normal concentration within 24 hours. The extremely sensitive response of adrenal ascorbic acid to ACTH is now utilized as a means of bioassay of ACTH potency. The exact relationship between ascorbic acid and the corticosteroids has not yet been established. The most striking morphologic change observed in the glands is hypertrophy. Sayers has stressed the fact that the reactions mentioned above must be looked upon as dynamic mechanisms which produce varying results depending upon the intensity and duration of the stimulus.

The significance of these observations is underscored by the fact that similar biochemical and morphological changes can be induced in the adrenals by a variety of situations which subject the animal to stress. Among the experimentally induced stress situations have been acute hemorrhage, exposure to extreme cold, scalding, stimulation of sensory nerves, operative procedures, injection of killed *B. coli*, and simulated altitudes of 20,000 feet. A variety of drugs, including histamine, epinephrine, ether, chloroform, etc., can also produce these effects. Similar treatment of previously hypophysectomized rats fails to produce a reduction of the cholesterol and ascorbic acid content of the adrenals. Long<sup>12</sup> believes that the common denominator

<sup>14</sup> LI, C. H., EVANS, H. M., and SIMPSON, M. E.: The adrenocorticotrophic hormone, *Jr. Biol. Chem.*, 1943, cxlix, 413.

<sup>15</sup> SAYERS, G., WHITE, A., and LONG, C. N. H.: Preparation and properties of pituitary adrenotropic hormone, *Jr. Biol. Chem.*, 1943, cxlix, 425.

<sup>16</sup> SAYERS, G., and SAYERS, M. A.: The pituitary-adrenal system, *Ann. N. Y. Acad. Sci.*, 1949, lv, 522.

uations, active participation of the anterior pituitary and adrenal cortex occupies a position of central significance. Selye has pointed out that the alarm reaction, however, is only one aspect, i.e. the first stage, of a syndrome which he calls the general adaptation syndrome. The other phases are the stage of resistance and the stage of exhaustion. In a comprehensive review, this investigator discusses the possibility that a variety of diseases such as hypertension, nephrosclerosis, rheumatic fever, and rheumatoid arthritis, to mention but a few, may be "diseases of adaptation" resulting from excessive or abnormal adaptive efforts involving the pituitary-adrenal system. With the expectation of an increased availability of purified hormones in the not too distant future these important concepts should offer fruitful sources for further intensive experimental investigation.

M. S. S.

but is incomplete since the following three sections on "Tuberculosis," "Venereal Disease" and "Tropical Diseases" should be included under this heading. It seems misleading to classify such diseases as bacillary dysentery, amebic dysentery, typhus fever, rabies, malaria, and "effects of heat" as tropical diseases. Certainly, they are all illnesses found in nontropical areas, and it is unfair to stress them as regional diseases, especially to students. The pneumonias are separately grouped under "Diseases of the Lungs."

There is a section on the Diseases of Infants. Rickets is discussed in this section. The other vitamin deficiency diseases are included under "Diseases of Metabolism." There is no mention of vitamin A deficiency.

The subject matter is often handled with such brevity as to render it useless to all intent and purpose. So far as the reviewer can determine, no mention is made of tularemia, torulosis, ornithosis, acute arteritis, toxoplasmosis, porphyria, Haverhill fever, and splenic neutropenia.

This textbook is not impressive in either its organization or content.

E. C.

*An Atlas of Electrocardiography.* By WILLIAM DRESSLER, M.D., Cardiologist, Maimonides Hospital, Brooklyn, Consultant in Cardiology, The Brooklyn Hospital, Lecturer in Medicine, Long Island College of Medicine; and HUGO ROESLER, M.D., F.A.C.P., Cardiologist, Department of Medicine, Associate Professor of Radiology, Temple University Medical School and Hospital. 503 pages, 27.5 × 21 cm. Charles C. Thomas, Springfield, Ill. 1949. Price, \$14.00.

This atlas is intended for those already conversant with the fundamentals of electrocardiography. Section I deals with electrocardiographic patterns excluding rhythm disturbances. Section II is devoted to disturbances of rhythm. Section III is concerned with advances in the electrocardiographic diagnosis of myocardial infarction. Section IV is a short section on unipolar leads.

In the first two sections, tracings which display similar patterns are arranged together, and the differential diagnosis is discussed. A summary of the clinical data is presented in addition to the electrocardiographic comment. This arrangement is valuable for teaching purposes and is commended. The section on disturbances of heart rhythm is especially good.

Most of the precordial leads shown are CF or CR; there are comparatively few records with V leads. The discussion of inverted T waves in Lead III makes no mention of variation of  $T_2$  with respiration, and no example of this common finding is shown. Statements are made concerning the localization of myocardial damage which are based upon the electrocardiograms shown, which in some instances are such that pathological confirmation would seem desirable. The records interpreted as indicating anterior myocardial infarction in the presence of left bundle branch block are very interesting, and would prove more valuable were postmortem studies available. The authors devote a good deal of space to records with the " $T_1$  smaller than  $T_3$ " pattern. They state that notching of T is probably equivalent to inversion of T. There are occasional references to certain electrocardiographic findings as reflecting "a positional peculiarity of the heart"; but more specific details of position or supporting information are not presented.

This text generally is interesting and informative, and possesses many virtues. These overshadow minor faults, which will probably disappear in future editions.

S. S.

- Bentley's Text-book of Pharmaceutics.* 5th ed. Revised by HAROLD DAVIS, B.Sc., Ph.D. (Lond.), Ph.C., F.R.I.C., Pereira Medallist, Sometime Chief Pharmacist, University College Hospital, London, with the collaboration of M. W. PARTRIDGE, B.Pharm., B.Sc., Ph.D. (Lond.), Ph.C., Lecturer in Chemistry, University of Nottingham, and A. I. ROBINSON, Ph.C., Late Pharmacist in Charge, Manufacturing Laboratory, Messrs. Stafford Allen & Sons, Ltd., London, with contributions by W. A. BROOM, B.Sc. (Lond.), F.R.I.C., M. ELLIS, M.Sc. (Wales), F.L.S., and H. A. TURNER, B.Sc. (Lond.), Ph.C., D.B.A. (Pharm. Soc.), Pereira Medalist. 1100 pages;  $22.5 \times 14.5$  cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$7.50.
- Clinical Biochemistry.* 4th ed. By ABRAHAM CANTAROW, M.D., Professor of Biochemistry, Jefferson Medical College, etc., and MAX TRUMPER, Ph.D., Commander, H(S), USNR., Lecturer in Clinical Biochemistry and Basic Science Coordinator, Naval Medical School, National Naval Medical Center, Bethesda, Maryland. 642 pages;  $24 \times 15.5$  cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$8.00.
- Fundamentals of Otolaryngology: A Textbook of Ear, Nose and Throat Diseases.* By LAWRENCE R. BOIES, M.D., Clinical Professor of Otolaryngology, Director of Division of Otolaryngology, University of Minnesota Medical School, and Associates: CHARLES E. CONNOR, M.D., ANDERSON C. HILDING, M.D., JEROME A. HILGER, M.D., JOHN J. HOCHFILZER, M.D., CONRAD J. HOLMBERG, M.D., KENNETH A. PHELPS, M.D., ROBERT E. PRIEST, M.D., and GEORGE M. TANGEN, M.D. 443 pages;  $24 \times 15.5$  cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$6.50.
- Gemeinsame Erkrankungen aus der inneren Medizin und Chirurgie.* By WALTHER KANERT and KURT AUGUST KOELSCH. 500 pages;  $24.5 \times 17.5$  cm. 1949. Georg Thieme Verlag, Stuttgart. Price, geb. DM 35.—
- Hemorrhagic Disorders: A Guide to Diagnosis and Treatment.* By PAUL M. AGGELER, M.D., Assistant Clinical Professor of Medicine, and S. P. LUCIA, M.D., Professor of Medicine, University of California Medical School. Lettered and illustrated by PHYLURIA GIBBS, HELENE CLEARE and JEAN THOMPSON, under the supervision of RALPH SWEET. 112 pages;  $28 \times 22$  cm. 1949. The University of Chicago Press, Chicago. Price, \$10.00.
- Lehrbuch der inneren Medizin.* By DR. ERNST LAUDA. 569 pages;  $25 \times 17.5$  cm. 1949. Springer-Verlag, Vienna. Price, \$7.20.
- Medical Clinics on Bone Diseases: A Text and Atlas.* 2nd ed. By I. SNAPPER, M.D., formerly Professor of Medicine, University of Amsterdam, The Netherlands, etc. 308 pages;  $28.5 \times 22$  cm. 1949. Interscience Publishers, Inc., New York. Price, \$20.00.
- Medizin in Bewegung: Klinische Erkenntnisse und ärztliche Aufgabe.* By RICHARD SIEBECK. 520 pages;  $24.5 \times 17$  cm. 1949. Georg Thieme Verlag, Stuttgart. Price, geb. DM 27.—
- Memories of Eighty Years.* By JAMES B. HERRICK. 270 pages;  $23 \times 15.5$  cm. 1949. The University of Chicago Press, Chicago. Price, \$5.00.
- Nervous and Neurohumoral Regulation of Intestinal Motility.* By W. B. YOUMANS, Professor of Physiology, University of Oregon Medical School. 129 pages;  $24 \times 15.5$  cm. 1949. Interscience Publishers, Inc., New York. Price, \$4.75.

- Subalimentación crónica y Esprue.* By DR. ARSACIO PEÑA YÁÑEZ. 189 pages; 25.5 × 18 cm. (paper-bound). 1949. Editorial Científico Medica, Barcelona, Spain.
- A Synopsis of Medicine.* 9th ed. By SIR HENRY LETHEBY TIDY, K.B.E., M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (Lond.), Extra Physician to H.M. The King, etc. 1243 pages; 19 × 12.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$7.50.
- A Text-book of Pharmacognosy.* 5th ed. By GEORGE EDWARD TREASE, B.Pharm., Ph.C., F.R.I.C., F.L.S., Reader in Pharmacognosy and Head of the Department of Pharmacy in the University of Nottingham. Revised with the assistance of H. O. MEEK, Ph.C., H. E. STREET, B.Sc., Ph.D., Ph.C., and E. O'F. WALSH, B.Sc., Ph.D., A.R.I.C., Ph.C. 811 pages; 22.5 × 14.5 cm. 1949. The Williams and Wilkins Company, Baltimore. Price, \$8.00.
- Tom Cullen of Baltimore.* By JUDITH ROBINSON. 435 pages; 23.5 × 16 cm. 1949. Oxford University Press, New York. Price, \$3.50.
- Von der Angst der Kranken.* By PROF. DR. MED. KARL SCHEELE. 76 pages; 21 × 14.5 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart. Price, kart. DM 4.80.
- A Year With Osler—1896-1897. Notes taken at his Clinics in The Johns Hopkins Hospital.* By JOSEPH H. PRATT, a Member of the Class of 1898. 209 pages; 23.5 × 15.5 cm. 1949. The Johns Hopkins Press, Baltimore. Price, \$4.00.

WILLIAM H. RISER, JR., M.D., Associate Professor of Medicine.  
 G. HARMON STOKES, M.D., Former Resident in Hematology, Jefferson-Hillman Hospital.

### *Visiting Faculty*

GOULD A. ANDREWS, M.D., Chief of Hematology, Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn.  
 W. R. ARROWSMITH, M.D., Instructor in Medicine, Tulane University of Louisiana School of Medicine, New Orleans, La.  
 IVAN W. BROWN, JR., M.D., Instructor in Surgery, Duke University School of Medicine, Durham, N. C.  
 MARSHALL BRUCER, M.D., Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn.  
 W. J. DARBY, M.D., Professor of Biochemistry and Assistant Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.  
 L. W. DIGGS, M.D., Professor of Medicine, University of Tennessee College of Medicine, Memphis, Tenn.  
 CHARLES M. HUGULEY, JR., M.D., Instructor in Medicine, Emory University School of Medicine, Emory University, Ga.  
 EDGAR JONES, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.  
 R. WAYNE RUNDLES, M.D., Associate in Medicine, Duke University School of Medicine, Durham, N. C.  
 HOWARD E. SKIPPER, Ph.D., Associate Director and Director of the Division of Biochemistry, Southern Research Institute, Birmingham, Ala.

This is a new course on the College schedule. It is especially scheduled to meet a demand to furnish advanced instruction in the field of Hematology to physicians in the Southeastern part of the country. Outstanding authorities are being invited from the University of Tennessee, Emory University, Vanderbilt University, Duke University, Tulane University of Louisiana and the Oak Ridge Institute of Nuclear Studies to join the faculty. Advanced instruction will be offered in the form of lectures, case reports and staff conferences in the mornings and laboratory studies in the afternoons.

The last day of the course, Saturday, December 10, will be devoted to the Southeastern Regional Meeting of The American College of Physicians comprising Alabama, Florida, Georgia, South Carolina and Cuba. Every registrant is urged to remain for the Regional Meeting. Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, is the General Chairman and Dr. Edgar G. Givhan, Jr., F.A.C.P., is Chairman of the Committee on Arrangements. The Regional Meeting program will be printed as a separate folder and will be supplied in advance to everyone in the course.

*Hotel Accommodations:* Tutwiler Hotel. Rates: Single rooms, \$3.50 to \$6.50; double rooms, \$5.50 to \$8.50; twin-bedded rooms, \$6.00 to \$8.50. Make reservations through Dr. D. O. Wright, 2930 North 16th St., P. O. Box 2603, Birmingham, Ala.

### OUTLINE OF COURSE

*Tuesday, December 6*

#### THE ANEMIAS

##### A.M. Session

8:30

Registration, Assembly and Announcements.

9:00- 9:30

Diagnosis and Treatment of Pernicious Anemia.

DR. JONES.

9:30-10:00

Diagnosis and Treatment of Nutritional Anemias.

DR. DARBY.

- 10:30-11:00 Treatment of Hemorrhagic Diseases.  
DR. DIGGS.
- 11:00-11:30 The Problem of Hypersplenism.  
DR. KRACKE.
- 11:30-12:00 Surgical Aspects of Portal Hypertension.  
DR. CHENOWETH.
- 12:00- 1:00 Clinico-pathological Conference.  
DRS. JONES and BAKER.

## P.M. Session

- 2:00- 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

*Friday, December 9*

## MISCELLANEOUS

## A.M. Session

- 9:00- 9:30 The Inheritance of Blood Diseases.  
DR. BUTTERWORTH.
- 9:30-10:00 Biopsy of the Liver.  
DR. RUNDLES.
- 10:00-10:30 Recent Advances in Transfusion Therapy.  
DR. BROWN.
- 10:30-11:00 Evaluation of Bone Marrow Patterns.  
DR. RISER.
- 11:00-11:30 The Inheritance of Red Cell Agglutinogens.  
DR. BUTTERWORTH.
- 11:30-12:00 Practical Aspects of the Rh Problem.  
DR. BROWN.
- 12:00-12:30 Tests for Malignancy as Applied to Hematology.  
DR. CLINE.
- 12:30- 1:00 Primary and Secondary Polycythemia.  
DR. RISER.

## P.M. Session

- 2:00- 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

*Note:* Discussions of all morning papers will take place during the Afternoon Sessions.

*Saturday, December 10*

## SOUTHEASTERN REGIONAL MEETING OF THE AMERICAN COLLEGE OF PHYSICIANS

The Annual Regional Meeting of the Southeastern States and Cuba will be held at Birmingham and the program is offered as an integral part of this postgraduate course.



- RICHARD S. COSBY, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- MARVIN DARSIE, M.D., Research Associate in Surgery, University of Southern California School of Medicine.
- SIM P. DIMITROFF, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- DOUGLAS R. DRURY, M.D., Professor of Physiology, University of Southern California School of Medicine.
- DONALD T. EDMEADES, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- HUGH A. EDMONDSON, M.D., Professor of Pathology, University of Southern California School of Medicine.
- STEPHEN R. ELEK, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- EDWARD R. EVANS, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- H. RUSSELL FISHER, M.D., F.A.C.P., Professor of Pathology, University of Southern California School of Medicine.
- HARRY GOLDBLATT, M.D., Professor of Pathology, University of Southern California School of Medicine.
- GEORGE C. GRIFFITH, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California School of Medicine.
- ERNEST M. HALL, M.D., F.A.C.P., Professor of Pathology, University of Southern California School of Medicine.
- ARTHUR M. HOFFMAN, M.D., F.A.C.P., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.
- RALPH E. HOMANN, JR., M.D., Assistant Professor of Medicine, University of Southern California School of Medicine.
- ROBERT W. HUNTINGTON, JR., M.D., Associate Professor of Pathology, University of Southern California School of Medicine.
- JOHN C. JONES, M.D., F.A.C.S., Associate Clinical Professor of Surgery, University of Southern California School of Medicine.
- JULIUS KAHN, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.
- DAVID C. LEVINSON, M.D., Research Associate, Department of Cardiology, University of Southern California School of Medicine.
- MOREY L. LIPKIS, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- ALBERTO MARIANACCI, M.D., Head, Electro-encephalography Department, Los Angeles County Hospital.
- HELEN E. MARTIN, M.D., Associate Professor of Medicine, University of Southern California School of Medicine.
- LOUIS E. MARTIN, M.D., F.A.C.P., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.
- VERNE R. MASON, M.D., Clinical Professor of Medicine, University of Southern California School of Medicine.
- EDGAR F. MAUER, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- PERRY J. MELNICK, M.D., F.A.C.P., Associate Professor of Pathology, University of Southern California School of Medicine.
- HAROLD MILLER, M.D., Fellow, Department of Cardiology, University of Southern California School of Medicine.
- HYMAN MILLER, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.

technics will be discussed from the physiologic and clinical standpoints. Roentgenology, electrocardiography and cardiac catheterization will be presented from the primary viewpoint of the underlying altered physiology.

Five clinical pathological conferences will emphasize the differential diagnosis of heart disease. There will be five clinical sessions in which cases illustrating physiologic problems such as dyspnea, cyanosis, pain, edema and heart failure will be studied.

The technic and value of cardiac catheterization, anticoagulants, and newer therapeutic trends will be fully covered.

*Hotel Accommodations:* The Biltmore Hotel, Mr. Francis Bustillo, Convention Manager, Los Angeles 13, Calif. Rates: Single rooms, \$7.00-\$8.00 daily; double or twin-bedded rooms, \$13.50 daily.

Alexandria Hotel, Mr. Frank Walker, General Manager, 5th and Spring Sts., Los Angeles 13, Calif. Rates: Single rooms with bath, \$5.00-\$6.00 daily; double rooms with bath, \$7.50 daily; twin-bedded rooms with bath, \$8.50 daily.

The above hotels are located near one another and are equally convenient to the meeting place of the course. In making reservations, identify yourself with The American College of Physicians and this particular course.

#### OUTLINE OF COURSE

*Monday, December 5*

##### A.M. Session

9:00- 9:15 Registration.

9:15- 9:30 Orientation.

B. O. RAULSTON, M.D., Dean, School of Medicine.

PHOEBUS BERMAN, M.D., Medical Director, Los Angeles County Hospital.

9:30- 9:50 Physiology of Dyspnea.

Dr. HOMANN.

9:50-10:05 Clinical Aspects of Dyspnea.

Dr. NORWOOD.

10:05-10:20 The Mechanism and Radiation of Coronary Artery Pain.

Dr. GRIFFITH.

10:20-10:40 Differential Diagnosis of Chest Pain.

Dr. COSBY.

10:40-11:00 The Physiologic Basis of Drugs Used in Coronary Pain.

Dr. ELEK.

11:00-11:20 The Prevention and Rehabilitation of Coronary Thrombosis.

Dr. KAHN.

11:20-12:00 New Instrumentation in Cardiovascular Physiology.

Dr. DRURY.

##### P.M. Session

1:00- 2:00 Clinical Pathological Conference.

DRS. EDMONDSON and MASON.

2:00- 3:00 Pain Clinic.

Case—Parietal Pain.

Dr. GRIFFITH.

Case—Coronary Insufficiency.

Dr. ROSENOW.

Case—Acute Myocardial Infarction.

Dr. SHEINKOFF.

Case—Dissecting Aneurysm of the Aorta.

Dr. EDMEADES.

- 10:05-10:20 Acyanotic Heart Disease in Cardiac Catheterization.  
DR. LEVINSON.
- 10:20-10:40 Cyanotic Heart Disease in Cardiac Catheterization.  
DR. COSBY.
- 10:40-10:50 Electrocardiogram during Cardiac Catheterization.  
DR. ZINN.
- 10:50-11:00 Summary of Studies.  
DR. GRIFFITH.
- 11:00-12:00 Cardiac Arrhythmias.  
DRS. PRINZMETAL and CORDAY, and STAFF.

## P.M. Session

- 1:00- 2:00 Clinical Pathological Conference.  
DRS. HUNTINGTON and LOUIS E. MARTIN.
- 2:00- 3:00 Rheumatic Heart Disease.  
Case—Rheumatic Fever.  
DR. GRIFFITH.  
Case—Mitral Stenosis with Auricular Fibrillation.  
DR. ASKEY.  
Case—Aortic Insufficiency and Mitral Stenosis.  
DR. LIPKIS.
- 3:00-3:30 Etiology and Pathogenesis of Rheumatic Fever.  
DR. GRIFFITH.
- 3:30- 4:00 The Diagnosis of Rheumatic Fever.  
DR. MARTIN.

*Thursday, December 8*

## A.M. Session

- 9:00- 10:30 Humoral Mechanism of Hypertension.  
DR. GOLDBLATT.
- 10:30-10:45 Early Renal Lesions Predisposing Hypertension.  
DR. BOYD.
- 10:45-11:00 Psychic Aspects of Hypertension.  
DR. PAGE.
- 11:00-12:00 Clinical Electrocardiographic Pathologic Conference.  
DR. THOMPSON.

## P.M. Session

- 1:00- 2:00 Clinical Pathological Conference.  
DRS. FISHER and HELEN E. MARTIN.
- 2:00- 2:30 Congenital Clinic.  
Case—Patent Ductus Arteriosus.  
DR. GRIFFITH.  
Case—Coarctation of Aorta.  
DR. BREM.  
Case—I. A. Septal Defect.  
DR. COSBY.  
Case—Tetralogy of Fallot.  
DR. CLELAND.
- 2:30- 3:00 The Differential Diagnosis of Congenital Heart Disease.  
DR. MARTIN.
- 3:00- 4:00 Surgery of Congenital Heart Disease.  
DR. JONES.

All registrations must be entered through the central office of The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

The registration in other courses, now completed, on the Autumn program of the College was gratifying, attesting to the continued popularity of these excellent courses. The 1950 schedule is being prepared by the Advisory Committee on Postgraduate Courses and will be announced in the next issue of this journal.

### REGIONAL MEETINGS

#### Reports on Recent Meetings

*Eastern Canada and New England*—Montreal, September 23–24, 1949. This was a two-day Regional Meeting covering the New England States, the Maritime Provinces and the Province of Quebec. Dr. Arthur T. Henderson, F.A.C.P., Governor for Quebec, was General Chairman; Dr. E. H. Mason, F.A.C.P. was Chairman of the Committee on Arrangements, and Dr. J. S. L. Browne, F.A.C.P. was Chairman of the Program Committee. Governors of the participating New England States and the Maritime Provinces coöperated and an attempt was made to have speakers from each State or Province. The various Governors presided over different portions of the program. All meetings were held at the Windsor Hotel, but the last afternoon was given over to visits to the Institute of Experimental Medicine and Surgery at the University of Montreal, to the Osler Library of McGill University and to the Montreal General Hospital Institute for Special Research and Cell Metabolism. The program was as follows:

#### FRIDAY MORNING SESSION

##### *Presiding Officer*

CHESTER S. KEEFER, M.D., F.A.C.P.

##### *Governor for Massachusetts*

9:30–10:30 Adaptation Syndrome.

HANS SELYE, M.D., Ph.D. (by invitation), Director, Institute of Experimental Medicine and Surgery, Université de Montreal, and J. S. L. BROWNE, M.D., F.A.C.P., Professor of Medicine, McGill University, Montreal, P. Q.

10:30–11:00 Coronary Sclerosis and Pulmonary Hypertension.

EUGENE H. DRAKE, M.D., F.A.C.P., Portland, Maine.

11:00–11:30 Recent Developments in the Pathogenesis of Diabetes Mellitus.

MARTIN M. HOFFMAN, M.D., Ph.D. (by invitation), Assistant Professor of Medicine, McGill University, Montreal, P. Q.

11:30–12:00 Shunting of Cerebrospinal Fluid into Peritoneal Cavity.

W. V. CONE, M.D. (by invitation), Associate Professor of Neurosurgery, McGill University,

REVIS LEWIS, M.D. (by invitation), and

IRA JACKSON, M.D. (by invitation); Montreal, P. Q.

#### AFTERNOON SESSION

##### *Presiding Officer*

HERMAN A. LAWSON, M.D., F.A.C.P.

##### *Governor for Rhode Island*

2:00–2:30 The Use of Radioactive Isotopes in Medical Investigation and Treatment.

JOSEPH P. ROSS (by invitation), Boston, Mass.

- 11:15-11:45 Results of the Treatment of Hypertensive Vascular Disease by Sodium Restriction.  
MICHAEL DiMAIO, M.D. (by invitation), Providence, R. I.
- 11:45-12:15 Rickettsial Pox.  
JOHN F. DALY, M.D. (by invitation), Assistant Professor of Dermatology, University of Vermont, Burlington, Vt.

---

Papers, 20 minutes; 10 minutes for discussion.

---

*Western New York*—Buffalo, October 1, 1949. The Western New York Regional Meeting has been established over many years, and has grown to be a popular and exceedingly well-attended meeting. Enthusiasm is always high and attendance is exceptionally good. The meeting was held under the Governorship of Dr. Edward C. Reifenstein, F.A.C.P., Syracuse. Dr. Edward F. Driscoll, F.A.C.P., Buffalo, was Chairman of the Committee on Arrangements and Dr. Roy L. Scott, F.A.C.P., Buffalo, was Chairman of the Scientific Program Committee. All sessions were held at the Hotel Statler. 118 members and 73 guests were registered. The program was as follows:

#### MORNING SESSION

NELSON G. RUSSELL, SR., M.D., F.A.C.P.,  
Buffalo, N. Y.

#### *Presiding*

9:30 Liver Biopsy.

DRS. A. H. AARON, F.A.C.P., KORDEL TERPLAN, S. SANES, W. F. LIPP, W. H. CHAPPLE, A. R. LENZNER, and R. C. BAHN; Buffalo, N. Y.

9:50 The Use of Tetraethylthiuramdisulphide (Antabuse) in the Rehabilitation of the Alcoholic.

DRS. KENNETH GOLDSTEIN (Associate), L. OSBORNE, R. KIDDER, W. CORCORAN, and R. HUBBARD; Buffalo, N. Y.

10:10 Some Aspects of the Epidemiologic Problems of Rocky Mountain Spotted Fever on Long Island.

DR. JOHN K. MILLER (Associate), Albany, N. Y.

10:30 Coarctation of the Aorta.

DRS. NELSON G. RUSSELL, JR., F.A.C.P., and JOHN R. PAINE (by invitation); Buffalo, N. Y.

10:50 INTERMISSION.

RICHARD N. DENIORD, M.D., F.A.C.P.,

Buffalo, N. Y.

#### *Presiding*

11:00 Advances in Electrocardiography.

DR. GEORGE H. REIFENSTEIN (Associate), Syracuse, N. Y.

11:20 The Vascular Menace in Diabetes.

DR. CHARLES B. F. GIBBS, F.A.C.P., Rochester, N. Y.

11:40 Discussion by DR. REGINALD FITZ, Boston, Mass.

12:00 INTERMISSION.

12:30 LUNCHEON (Terrace Room).

Ward, F.A.C.P., acting as Chairman of the Entertainment Committee. The College membership in Mississippi is comparatively small but it is customary for every member to turn out for the annual Regional Meeting there. Their program was as follows:

*Presiding*

JOHN G. ARCHER, B.S., M.D., F.A.C.P.

Greenville, Mississippi

*Governor for Mississippi*

The Internist's Responsibility for the Elderly Surgical Patient.

W. K. PURKS, M.D., F.A.C.P., Vicksburg, Mississippi.

Coarctation of Aorta With Report of Two Cases Operated upon Successfully.

GAYDEN WARD, M.D., F.A.C.P.

GEORGE HARVEY, JR., M.D. (by invitation), Jackson, Mississippi.

Prognosis of Heart Disease.

BEN R. HENINGER, M.D., F.A.C.P., Gulfport, Mississippi.

Management of Congestive Heart Failure.

SAMUEL NADLER, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Tulane University, New Orleans, Louisiana.

Psychosomatic Medicine.

JAMES F. LEWIS, M.D., F.A.C.P., Columbus, Mississippi.

Amyloid Disease.

DOUGLAS D. BAUGH, M.D., F.A.C.P., Columbus, Mississippi.

Lower Nephron Nephrosis. (*Acute Renal Failure.*)

WESLEY W. LAKE, M.D., F.A.C.P., Pass Christian, Mississippi.

The Problem of Hypersplenism.

ROY KRACKE, M.D. (by invitation), Dean, Medical College of Alabama, Birmingham, Alabama.

SOCIAL HOUR.

BANQUET (INFORMAL).

Toastmaster—MR. GEORGE GODWIN, Jackson, Mississippi.

Speaker—GOV. FIELDING WRIGHT, Governor of Mississippi.

Puerto Rico—Santurce, October 16, 1949. This was the first Regional Meeting ever formally organized in Puerto Rico. Dr. Rafael Rodriguez-Molina, F.A.C.P., as the Governor for the Island, organized the meeting and former President, Hugh J. Morgan, F.A.C.P., was the special representative from the Board of Regents. The program was as follows:

PROGRAM

*Presiding Officer*

RAMON M. SUAREZ, M.D., F.A.C.P., San Juan

Bleeding Tendency Due to Circulating Anticoagulants, with Report of a Case.

EDUARDO R. PONS, JR., M.D. (by invitation), and MERCEDES VICENTE DE TORREGROSA, Ph.D. (by invitation), San Juan City Hospital.

Pathogenesis of Schistosomiasis with Special Reference to Schistosomal Cirrhosis.

ENRIQUE KOPPISCH, M.D., F.A.C.P., Acting Director and Professor of Pathology, School of Tropical Medicine, San Juan.

## PROGRAM

Panel Discussion: Climatic Influence on Disease.

Climate and Respiratory Diseases.

KENT H. THAYER, M.D., F.A.C.P., Phoenix.

Climate and Metabolic Disturbances.

LESLIE B. SMITH, M.D., F.A.C.P., Phoenix.

Climate and Rheumatic Diseases.

HARRY E. THOMPSON, M.D., F.A.C.P., Tucson.

Discussion.

Early Diagnosis of Cor Pulmonale.

GEORGE C. GRIFFITH, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California, Los Angeles, California.

Biochemical Studies in Demyelinating Disease.

HAROLD H. JONES, M.D., F.A.C.P., Regent and Former Governor for Kansas of The American College of Physicians, Winfield, Kansas.

Recent Advances in The Treatment of Arthritis.

W. PAUL HOLBROOK, M.D., F.A.C.P., President, The Arthritis and Rheumatism Foundation, and DONALD F. HILL, M.D., F.A.C.P., Tucson.

Lower Abdominal Aneurysms.

LOUIS B. BALDWIN, M.D., F.A.C.P., Phoenix.

Non-tuberculous Intra-thoracic Lesions.

HAROLD KOHL, SR., M.D. (Associate), Tucson.

Necrotizing Arteritis Resulting from Generalized Fungus Infection.

ONIE O. WILLIAMS, M.D. (Associate), Director of the Clinical Laboratory and Pathologist, St. Joseph's Hospital, Phoenix.

Indications for Thoracotomy.

HOWELL S. RANDOLPH, M.D., F.A.C.P., Phoenix.

## EVENING

RECEPTION AND COCKTAILS.

DINNER (INFORMAL).

Toastmaster: ROBERT S. FLINN, M.D., F.A.C.P., Phoenix, President, Arizona State Medical Association.

Distinguished Guest Speakers:

HAROLD H. JONES, M.D., F.A.C.P., Regent, Winfield, Kansas. "The American College of Physicians—Present Trends."

GEORGE C. GRIFFITH, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California, Los Angeles, California. "Physiological Findings in Arteriovenous Aneurysms by Cardiac Catheterization Methods."

---

*Midwest Regional Meeting*—Indianapolis, November 19, 1949. Dr. J. O. Ritchey, F.A.C.P., Governor for Indiana, General Chairman, with the coöperation of the College Governors for Illinois, Iowa, Michigan, Minnesota, Ohio and Wisconsin. Dr. William S. Middleton, F.A.C.P., Madison, Wis., President-Elect, A.C.P., was the chief speaker at the banquet. Copy of the program is not available at the time this copy goes to press.

---

*New Jersey Regional Meeting*—Newark, November 30, 1949. Dr. George H. Lathrope, F.A.C.P., Governor for New Jersey, General Chairman; Dr. Johannes F. Pessel, F.A.C.P., Trenton, Chairman of the Program Committee; Dr. Jerome G. Kauf-

Emory University School of Medicine in coöperation with the Medical Association of Georgia offers annually a week's postgraduate course in Medicine and Surgery for general practitioners. The last such course was concluded on October 14, and was well attended by practitioners, particularly from the State of Georgia. The registration fee is \$10.00 for the week.

---

The New Jersey Fellows of the American Academy of Pediatrics in conjunction with the Medical Society of New Jersey and the New Jersey State Department of Health recently concluded a study of child health services in the State of New Jersey. The study covers county groups in New Jersey, ratio of children to physicians, distribution of children and physicians, general hospitals admitting children, location of general hospitals admitting children, child medical care in New Jersey on an average day, medical well-child conferences, distribution of health nurses and home visits, hospitals admitting polio patients, community mental hygiene clinics, etc. Dr. Harrold A. Murray, F.A.C.P., Newark, N. J., was the Study Director.

---

Yale University School of Medicine has initiated a series of short postgraduate courses in a coöperative program with the Connecticut State Medical Society in the Hartford Hospital. These courses are designed to give physicians an opportunity to become familiar with new knowledge, procedures, and point of view, and to assist them in practicing better medicine. Courses cover various fields of medicine and surgery.

---

#### ANNOUNCEMENT OF VAN METER PRIZE AWARD

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Houston, Texas, March 9 to 11, 1950.

The competing essays may cover either clinical or research investigations; may not exceed three thousand words in length, must be presented in English; and a typewritten, double spaced copy, in duplicate, sent to the Corresponding Secretary, Dr. George C. Shivers, 100 E. St. Vrain Street, Colorado Springs, Colorado, not later than January 15, 1950.

---

"The Place of Veterans Problems in Tuberculosis Control" was the subject of an address before the Southern Tuberculosis Conference at Memphis, Tennessee, September 15, 1949, by Dr. Leo V. Schneider, F.A.C.P., Chief of the Tuberculosis Control Section of the Veterans Administration, Tuberculosis Division, Washington, D. C.

---

Dr. J. A. Rosenkrantz (Associate) was promoted to Assistant Chief of Professional Services of the Kingsbridge Veterans Administration Hospital, Bronx, New York, during September.

---

#### CIVILIAN CONSULTANTS APPOINTED TO U. S. AIR FORCE MEDICAL SERVICE

Dr. W. Paul Holbrook, F.A.C.P., Tucson, Arizona, and Dr. Phillip T. Knies, F.A.C.P., Columbus, Ohio, have been appointed Consultants in Internal Medicine to the U. S. Army Air Force Medical Service. Dr. Charles E. Kossmann, F.A.C.P., New York City, has been appointed as Civilian Consultant in Cardiology.



## GEORGE MINOT LECTURESHIP

The Section on Experimental Medicine and Therapeutics of the American Medical Association recently established the George Minot Lectureship in honor of Dr. Minot's contributions to medical knowledge of the causes and methods of control of pernicious anemia. The first lecture will be arranged during 1950 or 1951. Dr. Minot (Boston) has been a Fellow of the American College of Physicians since 1928.

---

## COURSES IN POLIOMYELITIS

The University of Colorado Medical Center, aided by grants from the National Foundation for Infantile Paralysis, will give a series of postgraduate courses on Poliomyelitis, March 13-16, 1950, and May 22 to 27, 1950. The comprehensive care of patients in an epidemic will receive chief emphasis. Courses will be open to physicians west of the Mississippi River.

---

Dr. Thomas F. Walker, F.A.C.P., Great Falls, was recently installed as President of the Montana State Medical Association.

---

The Institute of Industrial Health of the University of Cincinnati conducted a course for physicians entitled "The Lead Problem in Industry," November 7 to 11, 1949. The course covered the background of the subject, of analytical and engineering considerations, inorganic lead intoxication, organic lead intoxication, economic and legal considerations. The class was limited to thirty-five physicians and the fee was \$50.00.

---

## SYMPOSIUM ON INHALATIONAL THERAPY

The Committee on Public Health Relations of the New York Academy of Medicine, in coöperation with the New York Association of Oxygen and Ambulance Services, will present a Symposium on Inhalational Therapy, consisting of exhibits, demonstrations, motion pictures, and lectures, at the Academy building, 2 E. 103rd Street, New York City, December 5 to 10, 1949. This course will bring to physicians interested in this field information about recent developments in this aspect of therapy and the efficient use of the equipment available for it.

---

Dr. J. Harry Murphy, M.D., F.A.C.P., was recently elected President of the Nebraska Tuberculosis Association.

---

A new periodical in an important field will begin publication in February 1950. It will be called "ANGIOLOGY, The Journal of Peripheral Vascular Diseases." Editor-in-Chief will be Dr. Saul S. Samuels, Chief of the Department of Peripheral Arterial Diseases, Stuyvesant Polyclinic, New York City.

Among Associate Editors in the United States are Dr. Alton Ochsner, of Tulane; Dr. Keith Grimson, of Duke; Dr. Leo Loewe, of Long Island Medical College; Dr. D. W. Kramer, of Jefferson; Dr. Gerald Pratt, of N. Y. University Medical School. A number of prominent foreign physicians will also serve. The Williams & Wilkins Company, of Baltimore, will be the publishers.

---

Dr. Joseph B. Kirsner, F.A.C.P., of the University of Chicago, has been elected President of the American Gastroscopic Society.

and are now serving internships will not be placed on active duty in the Regular Corps until completion of internship. Applicants for appointment in the grade of Senior Assistant Surgeon must meet the above requirements and must have had a total of at least 10 years of educational training and professional experience subsequent to high school. The entrance examination will include written professional tests, an oral interview, and a physical examination.

The professional written examination for the grade of Assistant Surgeon will cover the following subjects: 1. anatomy, physiology, biochemistry; 2. materia medica and therapeutics; 3. obstetrics and gynecology; 4. practice of surgery; 5. practice of medicine; 6. epidemiology and hygiene; 7. pathology and bacteriology. Senior Assistant Surgeon applicants will be examined on subjects 4, 5, 6, and 7 listed above.

Gross pay is governed by the Career Compensation Act of 1949, and is identical to that of officers of equivalent rank in the Army and Navy. Under current law, entrance pay for an Assistant Surgeon with dependents is \$5,686.56 per annum; for Senior Assistant Surgeon with dependents, \$6,546. These figures include the \$1,200 annual additional pay received by medical officers as well as subsistence and rental allowance.

Promotions. Provisions are made for promotion at regular intervals up to and including the grade of Senior Surgeon (Lt. Col.) and for selection for promotion to the grade of Medical Director (Col.).

Retirement pay after 30 years of service or at the age of 64, is three-fourths of annual base pay at the time of retirement. Retirement for disability is authorized under the Career Compensation Act and disability retirement pay is at a minimum, one-half of the annual base pay at the time of retirement.

Additional benefits include 30 days annual leave, sick leave, full medical care, and many of the usual privileges extended to members of the military forces.

Application forms and additional information may be obtained by writing to the Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C. Attention: Division of Commissioned Officers. Applications received after December 12, 1949, will not be accepted for this examination, but will be admitted to the examination in May, 1950.

morphological studies had been conducted a generation earlier, they would, no doubt, have contributed greatly to the progress of morphological and statistical genetics. As it was, they were conducted during the time when the study of heredity was leading into physiological and biochemical interpretations. Dr. Graves sensed this and with his accustomed insistent determination, he attempted to follow. Unfortunately, his health began to fail fully fifteen years ago, forcing him to place a limit on the incredibly long hours of devotion to the study which he had determined to make his life work. His mass of data and his osteological collection represent an expenditure of energy and time equalled to the knowledge of the writer by no other investigators, even by those who gave their full time to their research.

To know and understand Dr. Graves, one must understand and know not only his scientific and his clinical work but also his human characteristics, his kindness, his broad sympathies, his desire to alleviate suffering—a desire which had been enormously stimulated by reason of his own personal sufferings, his idealism and, above all, his ability to interpret favorably to the individual almost any kind of transgression. He was one of those rare individuals who applied in his own life the full truth of the proverb, "To know all is to excuse all." By nature and by choice, innately as well as by his education and by his self-discipline, he was a gentleman. His long period of failing health and his sufferings were terminated by death on April 19, 1949.

ALPHONSE M. SCHWITALLA, S. J., Dean Emeritus,  
St. Louis University School of Medicine.

#### DR. WILHELM S. ANDERSON

Dr. Wilhelm S. Anderson, F.A.C.P., Northfield, Minnesota, died June 26, 1949, at the age of 73, of coronary thrombosis. Dr. Anderson attended St. Olaf's College, then transferred to the University of Minnesota College of Medicine and Surgery from which he received his medical degree in 1903. He spent some periods of post-graduate study at Harvard Medical School and the New York Post-Graduate Medical School and Hospital. For a number of years he practiced medicine at Grand Forks, North Dakota. In 1927, he entered the U. S. Veterans Administration and served continuously in that service until his retirement about 1946. Dr. Anderson was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1931.

#### DR. THOMAS KRAPPFEL LEWIS

Thomas Krapfel Lewis, M.D., F.A.C.P., born in Merchantville, N. J., January 7, 1887, died in New Haven, Conn., August 28, 1949, of ventricular fibrillation, following an acute coronary occlusion five days previous.

His elementary education was received in the Merchantville public schools, following which he graduated from the New Jersey Friends' Academy of Moorestown, Haverford College in 1909, and the University of Pennsylvania School of Medicine in 1913. His internship was served at the Cooper Hospital, Camden, N. J., 1913-14.

As an internist he practiced in Camden, N. J., from 1914 until the time of his death, except for eighteen months while he served overseas in the First World War as Commanding Officer of the 165th Ambulance Company of the Rainbow Division.

Following his return from the army Dr. Lewis became active in civic, fraternal, and medical affairs. He was a Past President of the Camden Lions Club and a Past President of the Camden City and Camden County Medical Societies.

In 1921, he was appointed Attending Physician to the Cooper Hospital, and in 1946, he was elected Chief of the Medical Division of the Staff of this Hospital, which position he held until his death.

Association, a former president of the Decatur Medical Society and the Illinois State Tuberculosis Association. He had been a Fellow of the American College of Physicians since 1919 and served as Governor of the College for Southern Illinois since 1941.

A number of years ago, Dr. Jack initiated legal action and won the principle that the expenses for professional travel to scientific meetings shall be deductible from income in connection with the Federal Income Tax. This has saved physicians and allied professional men literally hundreds of thousands of dollars annually.

A smiling face and a warm handshake greeted his friends and colleagues at each and every meeting of the College, regional and national. He gave his time and effort in building the American College of Physicians and aided in selecting physicians who would be a credit to our College.

Dr. Jack was an outstanding internist in his community and his opinions were built on honesty and keen clinical judgment. We shall miss him as our true friend and Governor in Southern Illinois.

GEORGE W. PARKER, M.D., F.A.C.P.

### DR. PAUL EDWARD SIMONDS

Dr. Paul Edward Simonds, F.A.C.P., Riverside, Calif., died July 10, 1949, age 72. He was born in Detroit, Mich., October 12, 1876, pursued two years of collegiate work at Napa College and the University of Denver. He received his medical degree from the University of Southern California School of Medicine in 1908. He was a past Secretary, past Vice President and past President of the Riverside County Medical Association, past President of the Southern California Medical Association, a member of the California State Medical Association and of the American Medical Association. He had been a Fellow of the American College of Physicians since 1930, and he was a Diplomate of the American Board of Internal Medicine. His special interests were in the field of Internal Medicine and Geriatrics. In his later years, his practice was very limited. For more than twenty-five years, he had made a great contribution to the Boy Scout movement in the Riverside area. He was a family physician in the finest sense and contributed a great deal in keeping the practice of medicine in his county at a high level.

### DR. ROBERT EDWARD WESTMORELAND, SR.

Dr. Robert Edward Westmoreland, Sr., an Associate of The American College of Physicians since 1947, aged 40, Chief of the Medical Service at the Veterans Administration Hospital in Indianapolis, died June 30, 1949, at the Mayo Clinic in Rochester, Minnesota, of cardiac failure.

Dr. Westmoreland was born at Petersburg, Virginia, July 17, 1908. He received his B.S. from the University of Virginia in 1928 and his M.D. from the University of Virginia Department of Medicine in 1932. He interned from 1932 to 1934 at the New York Postgraduate Hospital, and thereafter was Assistant Physician to the Hospital and Attending Physician to the Dispensary for some years. He served in the Medical Corps, U. S. Army from 1942 to 1946, attaining the rank of Major. Thereafter, he entered the Veterans Administration and became Chief of the Medical Service at the Indianapolis Veterans Administration Hospital. He was a member of the New York County Medical Society, the State of New York Medical Society and the American Medical Association, and a diplomate of the American Board of Internal Medicine.

# ANNALS OF INTERNAL MEDICINE

VOLUME 31

DECEMBER, 1949

NUMBER 6

## THE ETIOLOGY AND MANAGEMENT OF THE HEMORRHAGIC DIATHESSES \*

By CHARLES A. DOAN, M.D., F.A.C.P., *Columbus, Ohio*

HEMORRHAGE uncontrollable except by expert medical management, may present in the practice of any physician at any time. Under normal conditions, the integrity of the vascular system and the circulating fluidity of the blood reflect a nice physiologic balance in an exceedingly sensitive and complicated coagulation mechanism. The physical-chemical intricacies of normal blood coagulation continue to challenge the best thought of many investigators and to stimulate ever more detailed experimentation in many laboratories, in the attempt to better understand and to more effectively solve the clinical problems centering about abnormal hemorrhage. The concepts and terminology arising from parallel efforts in different laboratories have resulted in much confusion among clinical diagnosticians regarding the interrelationships of the basic coagulation phenomena themselves. The first prerequisite, therefore, in approaching this field is a definition of terms, currently presumed to be interchangeable, as they have been coined to describe the observed sequence of events in normal blood coagulation (Graph A, page 981—modified after Quick) the exact chemical factors concerned having not yet been isolated.

It is now agreed that both platelets and plasma factors are essential for completely physiologic blood coagulation, Brinkhous and Conley each having demonstrated the lack of spontaneous coagulation of blood plasma for long periods when blood is carefully collected in silicone (methylchlorosilane) coated tubes, the blood platelets being promptly separated and the plasma stored at low temperatures ( $4^{\circ}$  C). Quick has hypothesized the liberation of an enzyme, thromboplastinogenase, from disintegrated platelets, which is essential for the conversion of plasma thromboplastinogen to thromboplastin (thrombokinese). Injured tissue may also be the source of thrombo-

\* Presented as a Morning Lecture at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 21, 1948. Received for publication September 8, 1949.

a synonym for the proteolytic enzyme activity which has been known variously as serum trypsin, serum tryptase, serum protease, fibrinolysin and thrombolysin. The streptococcic filtrate factor comparable in action on plasminogen or plasmogen has been called streptokinase, and the antibody-like resistance which may be demonstrated in certain patients recovered from streptococcic infections has been designated antistreptokinase. In the albumin fraction of plasma has been found an inhibiting enzyme, antiplasmin (Macfarlane).

Obviously a clinical bleeding tendency may occur under a wide variety of pathologic circumstances, and be influenced by one or more of many potential factors acting at any one of the many points in the complex mechanism of blood coagulation. The first clinical sign may appear and re-appear as an asymptomatic transitory purpuric manifestation, apparently limited to skin or mucous membranes, or the syndrome may present as one of the most acute, fulminant and critical emergencies with which the physician is ever called upon to deal. The specificity, and therefore the success of the therapeutic regimen advised, is directly dependent upon the preciseness and exactitude, and, in the acute purpuras, the promptness of the differential etiologic diagnosis in any given patient.

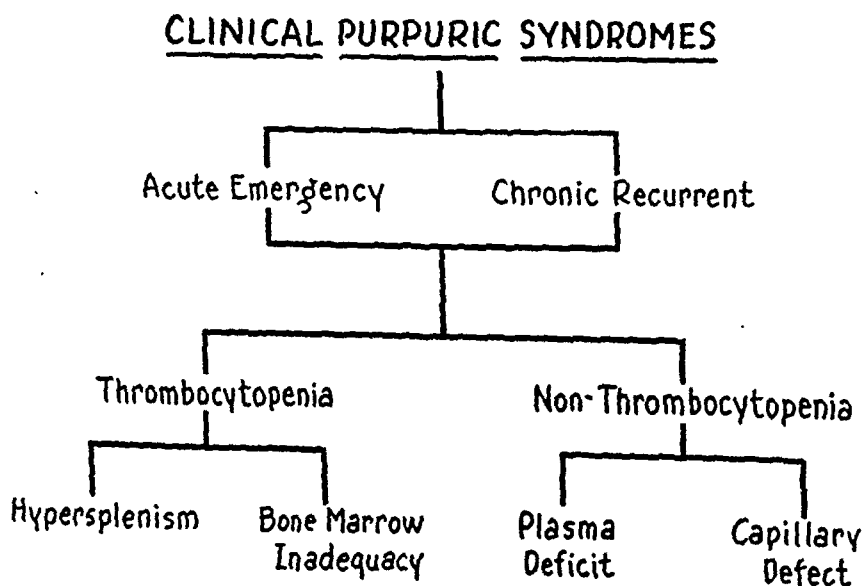


FIG. 1.

The approach to an understanding of the particular mechanism involved can best be made systematically, keeping in mind certain rather broad principles which underlie the hemorrhagic diatheses (figure 1). When a true purpuric extravasation of blood has been identified by its color, character and permanence, or if persistent bleeding occurs other than in the skin, it at once becomes essential to know whether the thrombocytes are normal or are decreased in the peripheral circulation.

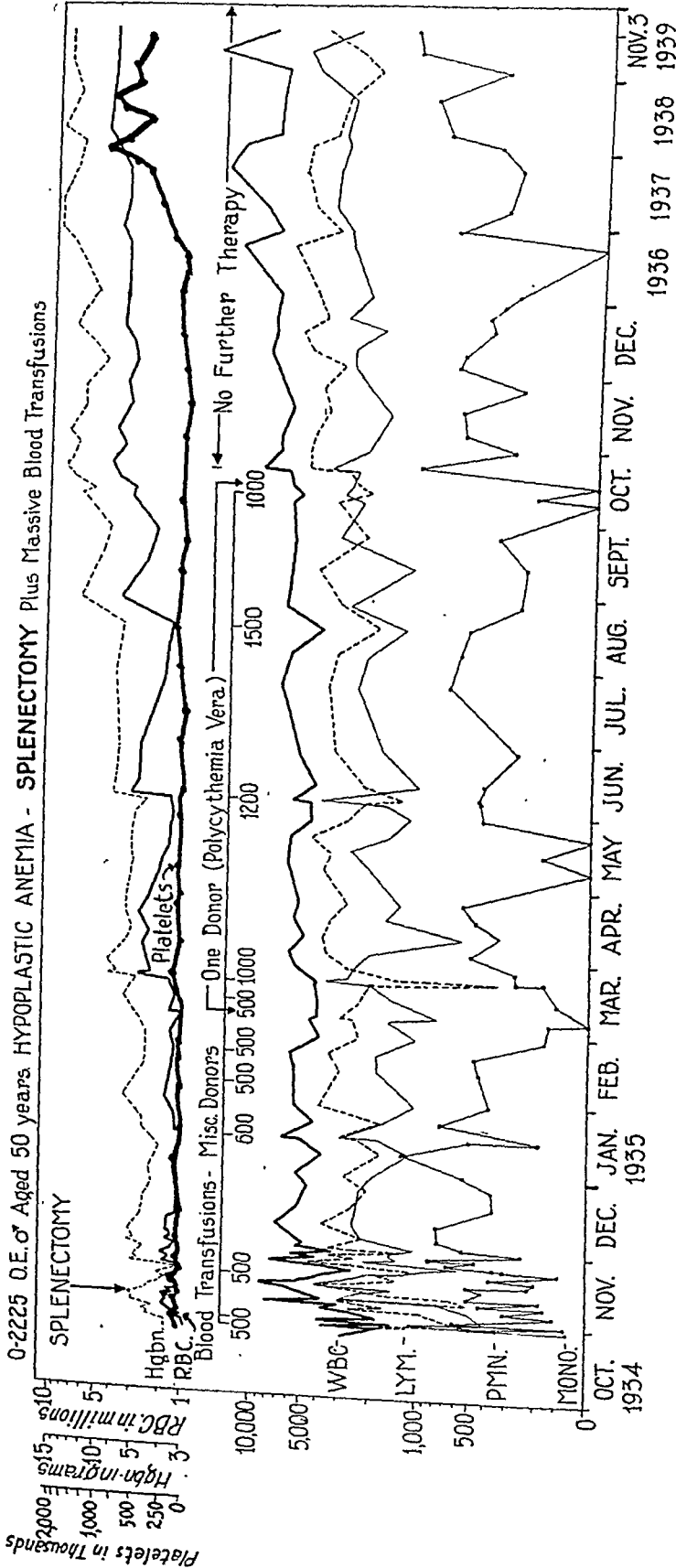


Fig. 3.

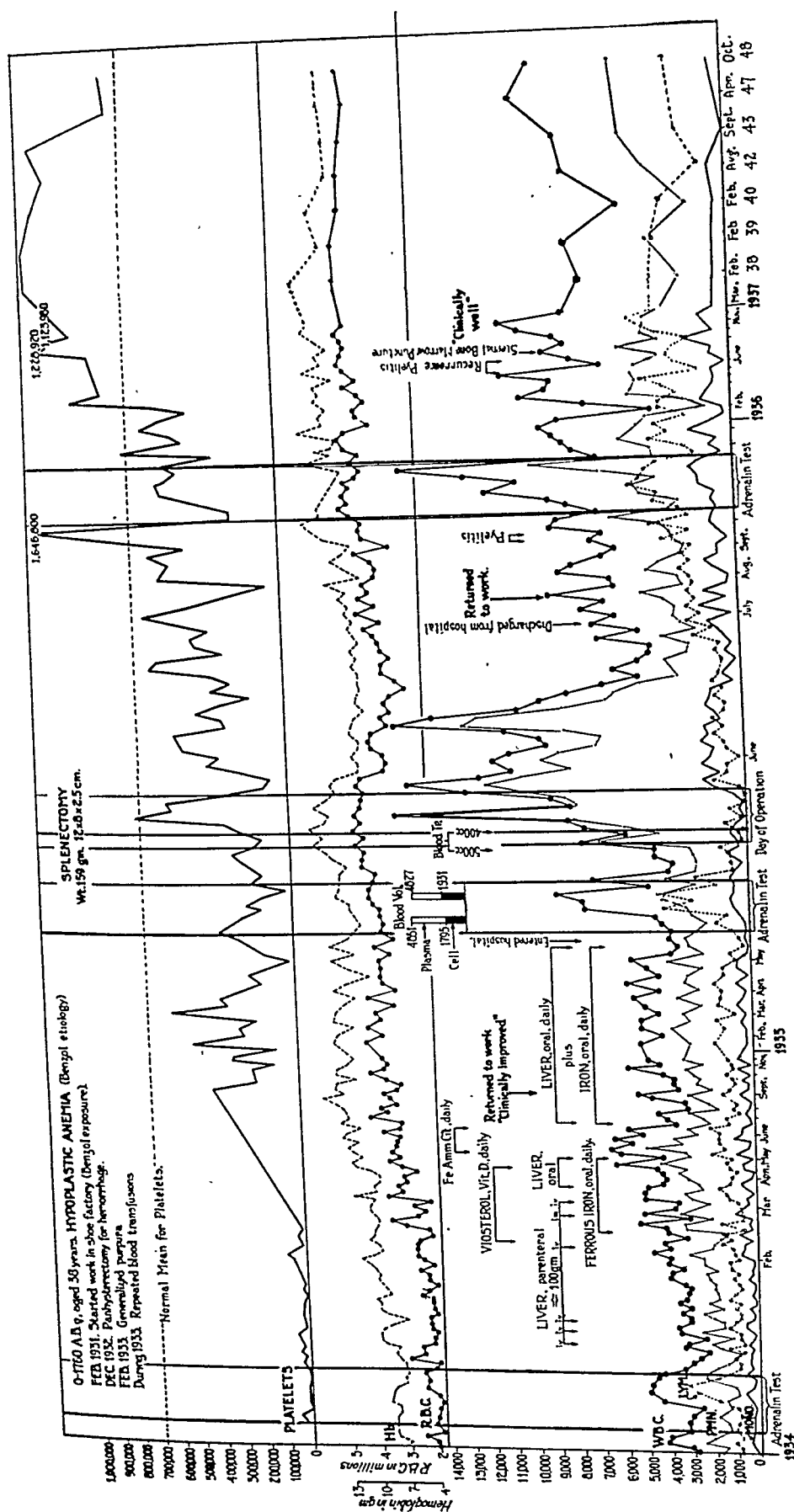


FIG. 4.



is not demonstrably enlarged, *primary splenic thrombocytopenic purpura* is the most likely diagnosis.

*Primary Hypersplenic Thrombocytopenic Purpura (Werlhof's Disease).* In the absence of any other demonstrable pathologic mechanism, specifically bone marrow damage or inadequacy, the adrenalin test may reveal an hypersequestration of platelets by a normal sized spleen indicative of a primary specific withdrawal or inhibition of circulating platelets (figure 6). Note that the postsplenectomy adrenalin test failed to reveal the hypersequestration

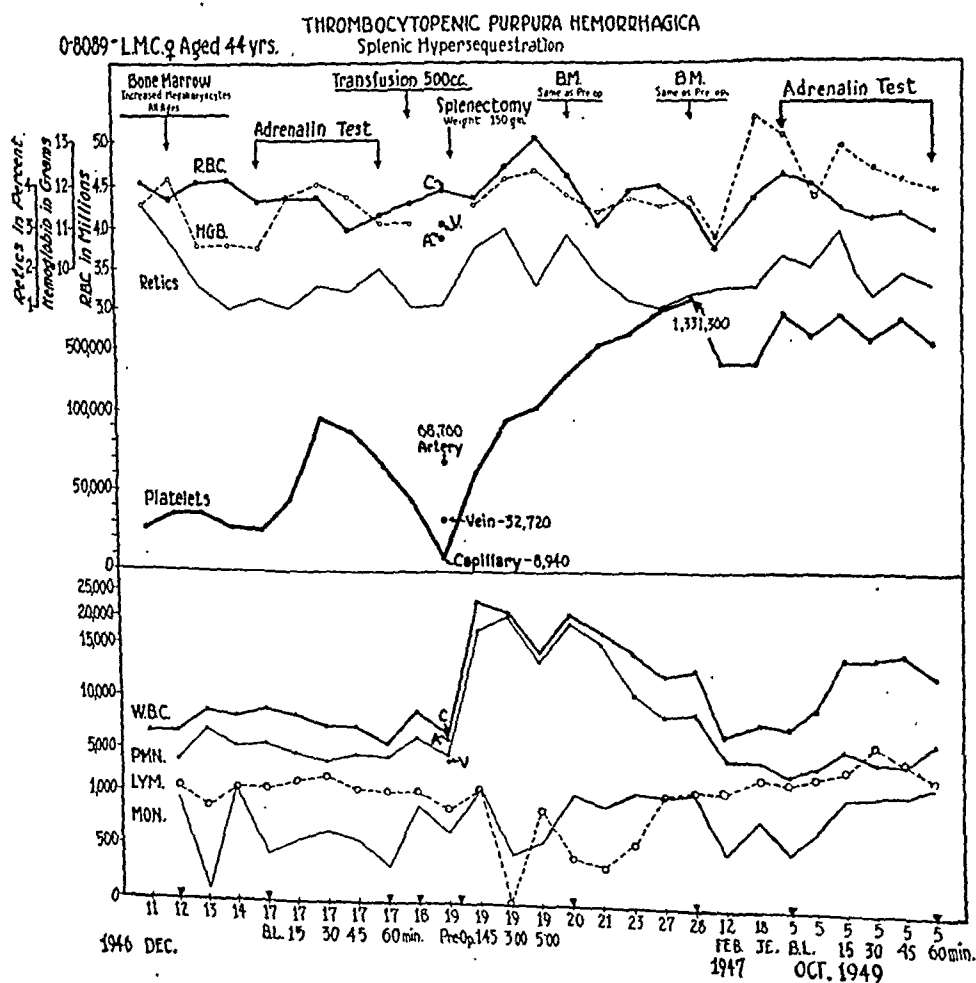


FIG. 6.

of thrombocytes, so well demonstrated during the purpuric episode. The clinical manifestations may be relatively benign, chronically recurring, chiefly cosmetic in the showering of skin petechiae, or they may develop suddenly and involve multiple critical hemorrhages involving mucous membranes of nose and mouth, gastrointestinal tract, genito-urinary system, uterus, and central nervous system. In the acute episode there may be time only for peripheral blood and bone marrow diagnostic studies. When there is severe headache, stupor, or other signs of increased pressure due to intracranial

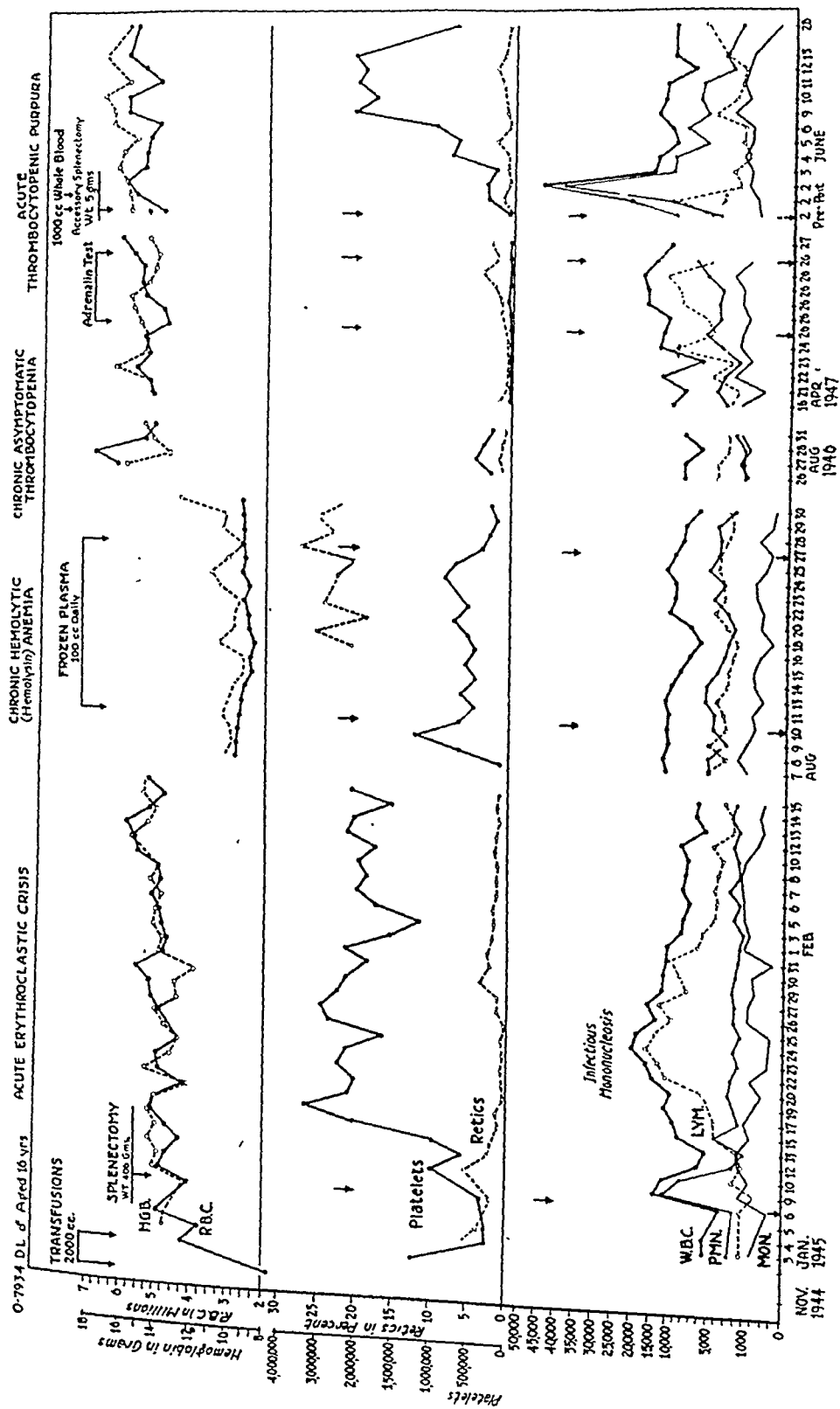


FIG. 7.

without evidence of liver or lymph node involvement. On supravital and fixed section study the pathology of Hodgkin's granuloma was revealed, apparently primary in the spleen. The specificity of the hypersequestration of platelets by this Hodgkin's involved spleen was proved by the dramatic and immediate rise in circulating platelets with improved blood coagulation, which was evident during the completion of the operation. Though unsuccessful in removing the sole focus of Hodgkin's, as we had hoped, other manifestations of the disease developing during the ensuing 18 months—there was never any recurrence of the thrombocytopenia or purpuric complications.

0-8887 55 g AGED 12 YRS. THROMBOCYTOPENIC PURPURA

- 1 Acute Rheumatic Fever with Cardiac Damage.
- 2 Bronchopneumonia → Acute Cardiac Failure.
- 3 Congestive Splenomegaly → Acute Hypersplenism.
- 4 Thrombocytopenic Crisis → Generalized Purpura
- 5 Bone Marrow Hyperplasia sans Toxic Damage

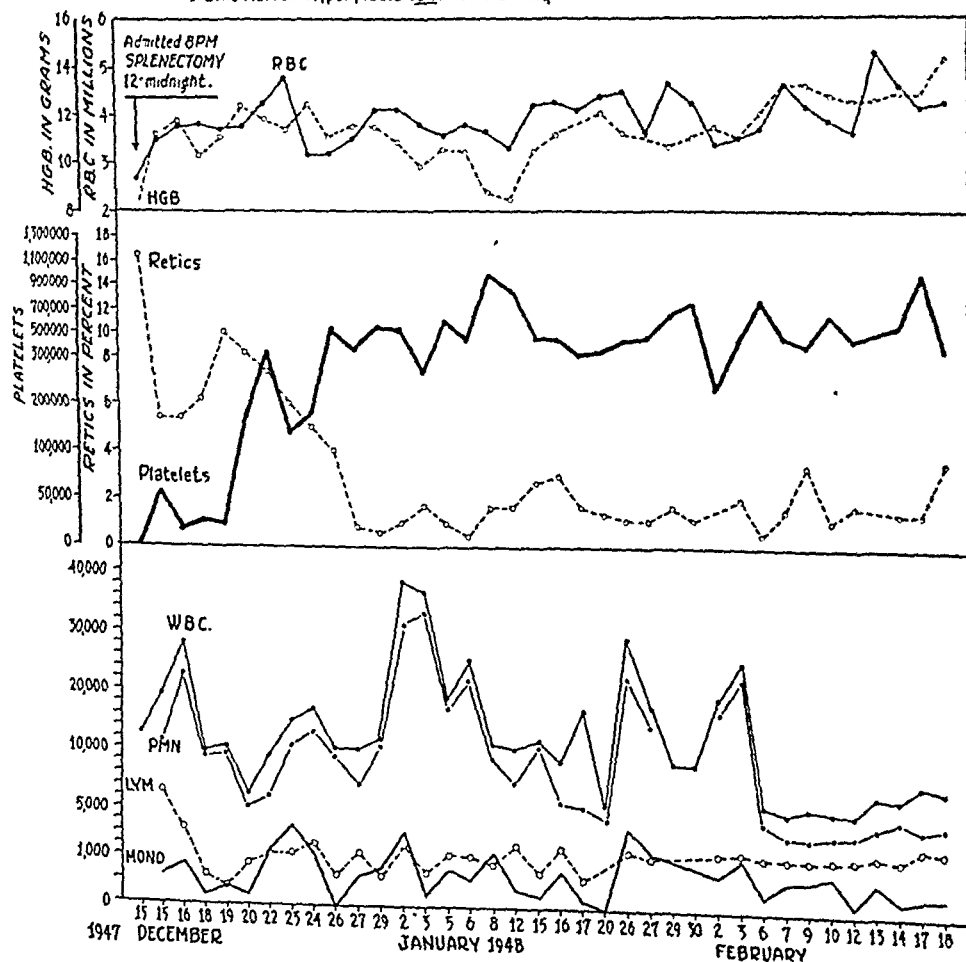


FIG. 9.

A young girl, aged 12 years, was admitted to the University Hospital as an acute emergency with generalized purpura, persistent epistaxis and gastrointestinal and genito-urinary hemorrhages of three days' duration (figure 9). Repeated fresh whole blood transfusions, prior to admission, had failed to control the hemorrhagic diathesis even temporarily. An acute upper respiratory infection with bilateral pneumonitis had preceded the bleeding manifestations and a toxic etiology, bacterial or chemotherapeutic in origin was suspected. Peripheral blood studies confirmed the complete absence of circulating platelets, and a coincidental supravital survey of the bone-

played by other mechanisms. Low prothrombin levels have been shown to be responsible for purpura in "melena neonatorum" or "hemorrhagic disease of the newborn" (as low as 5 per cent of normal adult level); in obstructive jaundice, the absence of bile from the intestinal tract interfering with optimum absorption of the fat-soluble vitamin K; in liver disease sufficiently severe to interfere with its important function of prothrombinogenesis from vitamin K; in individuals on a low vitamin K diet; and in patients with hyperperistalsis or other intestinal pathology preventing proper vitamin K absorption.

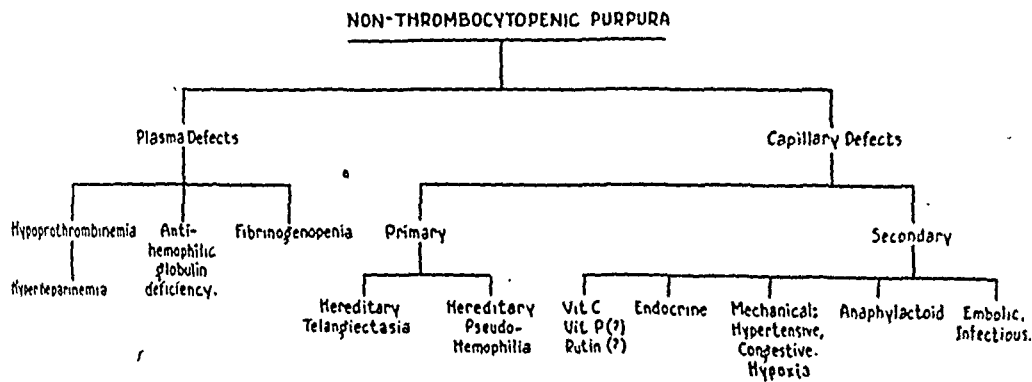
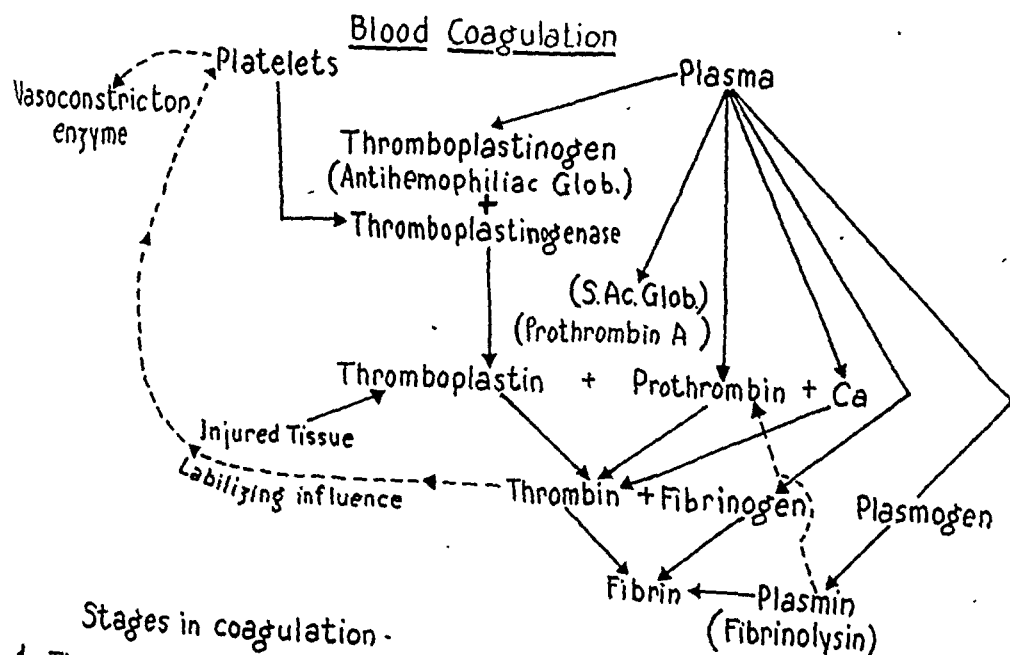


FIG. 10.



Stages in coagulation -

1.  $\text{Thromboplastinogen} + \text{platelet enzyme} \rightarrow \text{thromboplastin}$
2.  $\text{Prothrombin} + \text{thromboplastin} + \text{Ca} = \text{thrombin}$
3.  $\text{Fibrinogen} + \text{thrombin} \rightarrow \text{fibrin}$

Modified after Quick

GRAPH A.

may be necessary for the prevention of spontaneous hemorrhages in the normal course of living, and preceding elective surgery; or in the presence of trauma or emergency surgery rigid temporary control of the coagulation time may be mandatory, even life-saving.

Fresh whole blood, fresh plasma, or freshly frozen or lyophilized plasma obtained from "normal" donors, contains antihemophilic globulin, which will reduce the prolonged in vitro coagulation time of the blood from a hemophilic patient more or less to normal at once and for a variable period of time. The amount required and the frequency of readministration depend upon so many uncontrollable variables that only regularly repeated coagulation tests on carefully obtained samples of venous blood may determine these data for each individual patient, especially in times of critical need.

Plasma Fraction I of Cohn contains the largest increment of anti-hemophilic globulin, and may be used entirely effectively. It is available through the National American Red Cross. Again, however, no standard dosage can be recommended, (1) because of the variability of the potency of each lot prepared; (2) because of the variability in the hemophilic patient's own need from time to time; and (3) because of the greater antigenicity of Fraction I than whole blood.

Unless the very occasional patient should develop a specific "antibody-like" resistance to transfused normal human globulin, the sources of anti-hemophilic globulin, including fresh normal whole blood or human plasma are now such as to make possible the approach to this problem today with some equanimity and a greater assurance of success. In the more acutely susceptible individuals a regimen of regular prophylactic supplements of antihemophilic globulin-containing plasma may be established on a one to three day basis with some promise of success.

*Fibrinogenopenia.* The normal human plasma fibrinogen level ranges from 0.2 to 0.4 gm. per cent. Afibrinogenemia occurs rarely as a congenital and usually as a familial disease with the hemorrhagic tendency becoming apparent, and therefore, dangerous, only secondary to trauma. Fresh blood or plasma transfusions may be effectively used to supply the fibrinogen deficit.

Fraction I of Cohn contains the fibrinogen portion of the plasma and Diamond has reported its successful use as a prophylactic in the satisfactory control of patients with this defect when given regularly, for example in one of his patients, every three days. Each patient must, of course, be studied individually for dosage and frequency.

#### *Capillary Defects Resulting in Clinical Purpura.*

*Primary Hemorrhagic Telangiectasia.* Hereditary telangiectasis is a rather common, usually benign, hereditary abnormality, its pin-head sized or larger nodular vascular tumors and spider angiomas being more frequently of cosmetic than hemorrhagic concern. The bright red compressible capillary tufts in skin and mucous membranes have often been mistaken for the petechiae of true purpura on superficial examination. There is, however, no

to assist in decreasing capillary fragility in these patients, though its precise pharmacologic action has not been satisfactorily demonstrated. Optimum prompt coagulation of any extravasated blood must be assured through parenteral vitamin K therapy (4 to 10 mg. daily). Local or generalized hypoxia affects the functional integrity of endothelial cells as it does all other tissues and organs in the body, and when this danger of cell damage is added to the mechanical factors in congestive failure—oxygen therapy is urgently indicated, as it is in all other purpuras when a low oxygen tension in the tissues results from an excessive loss, or inadequate oxygenation, of the circulating hemoglobin.

*Anaphylactoid Purpura.* Purpura on the basis of an antigenic hypersensitization mechanism may occur: (1) secondary to specific megakaryocytic damage with a resultant thrombocytopenic purpura of central bone marrow origin; or (2) as the result of a generalized vascular endothelial sensitization, so-called "anaphylactoid purpura." A careful history, skin and dietary elimination tests for specific allergies may elicit one or more specific antigens which may then lead to avoidance or a specific desensitizing therapeutic regimen. More often than not, however, the antigenic specificity remains anonymous despite exhaustive testing.

When testing for a purpura producing antigen, a warning should be sounded relative to the extremely high degree of specific sensitization, which may develop in a patient to such drugs, for example, as Sedormid (see figure 5). In two instances in our own experience where this drug was suspected and an extremely small oral dose was repeated to establish it as the cause of a previous purpuric episode, a near fatal, generalized thrombocytopenic purpura was re-precipitated, lasting five to seven days, with widespread megakaryocyte damage. Forced fluids, to hasten elimination of the offending antigen, and supportive blood transfusions to supply platelets, are the treatment of choice and must be continued over the period required for megakaryocyte regeneration.

Lacking specific identification of the offending antigen, an autogenous urinary proteose concentrate may be obtained from such patients, during periods of active anaphylactoid purpuric exacerbations and, when antigenic specificity is demonstrated, through intracutaneous skin testing, a therapeutic desensitizing regimen may be instituted, which will induce, in some patients, a most gratifying remission for an indefinite period, even for years.

The anti-histaminic drugs may at times be helpful; for example, Benadryl capsules, 50 mg., three to four times daily for adults, the elixir 10 mg. to the dram for children; Pyribenzamine, 50 mg. tablets, elixir 5 mg. per dram; Neo-antigan 50 mg. dosage two to four times daily.

Histamine in the form of the diphosphate may be employed as a non-specific desensitizing antigen: initial dosage 0.1 mg. subcutaneously, to be gradually increased at two to seven day intervals to 1 mg., or 2 mg. in 250 c.c. NaCl may be given, intravenously very slowly. The maintenance dose is 1 mg. once weekly.

thrombocytopenia (figure 9). A non-hemorrhagic epidemic of enteritis, in community and home, had been communicated to the twins, each of whom promptly developed a marked bleeding diathesis with the infection. Again the circulating platelets were found to be extremely low or absent, but in this instance bone marrow studies revealed a central toxic picture affecting all cell types. The megakaryocytes were scarce and showed both nuclear and cytoplasmic degenerative vacuolization. Meticulous nursing care, supportive fresh whole blood transfusions and chemo- and antibiotic therapy resulted in the gradual regeneration of the essential marrow elements, followed by a return of platelets to the circulation with the permanent disappearance of all purpuric manifestations. Splenectomy under these circumstances would be fatal.

*Endocrine Deficiency.* Excessive uterine hemorrhage may occur as a part of any generalized purpuric syndrome in which platelet or plasma coagulation defects can be demonstrated, or it may present as a sometimes confusing, exsanguinating dysfunction, with minimal or no coagulation abnormalities, to be classified nevertheless as a "purpuric" manifestation. For immediate control, to arrest serious functional hyper- and polymenorrhea: (1) Ergotrate, grs. 1/320 every 4 to 12 hours, for not more than eight consecutive doses without 24 hr. rest period; (2) obstetrical pituitrin or pitocin, 1 ampoule, intramuscularly every 4 hrs., as long as necessary; (3) calcium gluconate or chloride, 10 c.c. 10 per cent solution intravenously. There is no incompatibility if the administration of all three of these agents is required in the same patient. For less urgent action effective within two to three days: testosterone 25 mg. per day; or antuitrin S, one or two ampoules daily; or stilbestrol, 5 to 10 mg. daily. A mild hypothyroid state is commonly associated with this syndrome and small doses of one-half to one gr. desiccated thyroid frequently are sufficient to readjust the responsible endocrine disequilibrium. Gynecologic consultation and examination are indicated when the hematologic coagulation mechanism has been eliminated as a precipitating or contributing factor in hypermenorrhea.

The informed physician and surgeon today may approach the patient with a hemorrhagic diathesis with a degree of assurance and confidence heretofore impossible, due to the increasing ease of quantitative evaluation and specificity of control of each individual factor in the complex physiologic mechanism of coagulation.

#### BIBLIOGRAPHY

- ALLEN, J. G., et al.: Abnormal bleeding, Jr. Am. Med. Assoc., 1949, cxxxix, 1251.  
 BRINKHOUS, K. M.: Clotting defect in hemophilia: deficiency in a plasma factor required for platelet utilization, Proc. Soc. Exper. Biol. and Med., 1947, lxvi, 117.  
 CONLEY, C. L., HARTMANN, R. C., and MORSE, W. I.: Clotting behavior of human platelet-free plasma: evidence for the existence of a "plasma thromboplastin," Jr. Clin. Invest., 1949, xxviii, 340.  
 DAVIDSON, C. S., EPSTEIN, R. D., MILLER, G. F., and TAYLOR, F. H. L.: Hemophilia: a clinical study of forty patients, Blood, 1949, iv, 97.  
 MACFARLANE, R. G., and BIGGS, R.: Fibrinolysis: its mechanism and significance, Blood, 1948, iii, 1167.  
 OWREN, P. A.: Coagulation of blood: investigations on a new clotting factor, Acta med. Scandinav., (Suppl. 194), 1947, cxxviii, 1-327.

# STUDIES ON THE MECHANISM OF CARDIAC INJURY IN EXPERIMENTAL HYPOTHERMIA \*

By KURT LANGE, M.D., DAVID WEINER, M.D., and MICHAEL M. A. GOLD, M.D., *New York, N. Y.*

THERE are numerous reports in the literature that subsequent to exposure to severe cold accompanied by a lowering of body temperature severe cardiac irregularities or sudden death may occur. These effects may occur even up to 24 hours after the exposure when the body temperature has long since returned to normal.<sup>1-6</sup> Such instances were encountered during the war with previous exposure to cold water (immersion) or with certain therapeutic uses of cold as an adjuvant in the treatment of malignancy. Numerous investigators have attempted to explain the hypothermic death but no single theory has found general acceptance.

Ariel, Bishop and Warren <sup>7</sup> report that in rabbits lowering of body temperature by immersion into cold water leads to a slowing of the heart rate with widening of the QRS complexes and marked prolongation of the S-T segments. Smith reports <sup>4</sup> similar observations in humans treated with cryotherapy and he states that death immediately after the therapy or within 24 hours is due to an anoxia caused by a decreased cardiac output. On autopsy of such patients who also had a marked reduction in respiratory rate neither the heart nor the cerebrum showed any remarkable changes. Clark <sup>8</sup> states that lowering of body temperature in the frog results in a reduction of heart rate, in a slowing of conduction, a decrease in force of contraction and a decrease in oxygen consumption. He states specifically that the rate is not a linear function of blood temperature in the rabbit or the frog. The most detailed data on the influence of lowered body temperature on the heart in humans are given by Kossmann <sup>5</sup> who noted the marked venous constriction which makes the taking of blood samples so difficult. He states that there is a linear relationship between body temperature and the length of the electrical systole as expressed by Bazett's formula. The T waves in his patients were markedly lowered with lowered body temperatures and the S-T segments became depressed. Auricular fibrillation was observed in four out of nine patients subjected to cryotherapy and Kossmann states that changes especially in the Q-T interval occurring in cooling may persist long beyond the lowering of body temperature. Tomaszewski <sup>6</sup> reports a case dying from exposure to cold in which the P-R interval and the intraventricular conduction time were

\* Received for publication December 16, 1948.

From the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals and the New York Medical College Research Unit (Metropolitan Hospital).

Carried out under a contract between the Research and Development Board of the Surgeon General, U. S. Army and the New York Medical College.



## RABBIT DURING TRENCHFOOT EXPOSURE

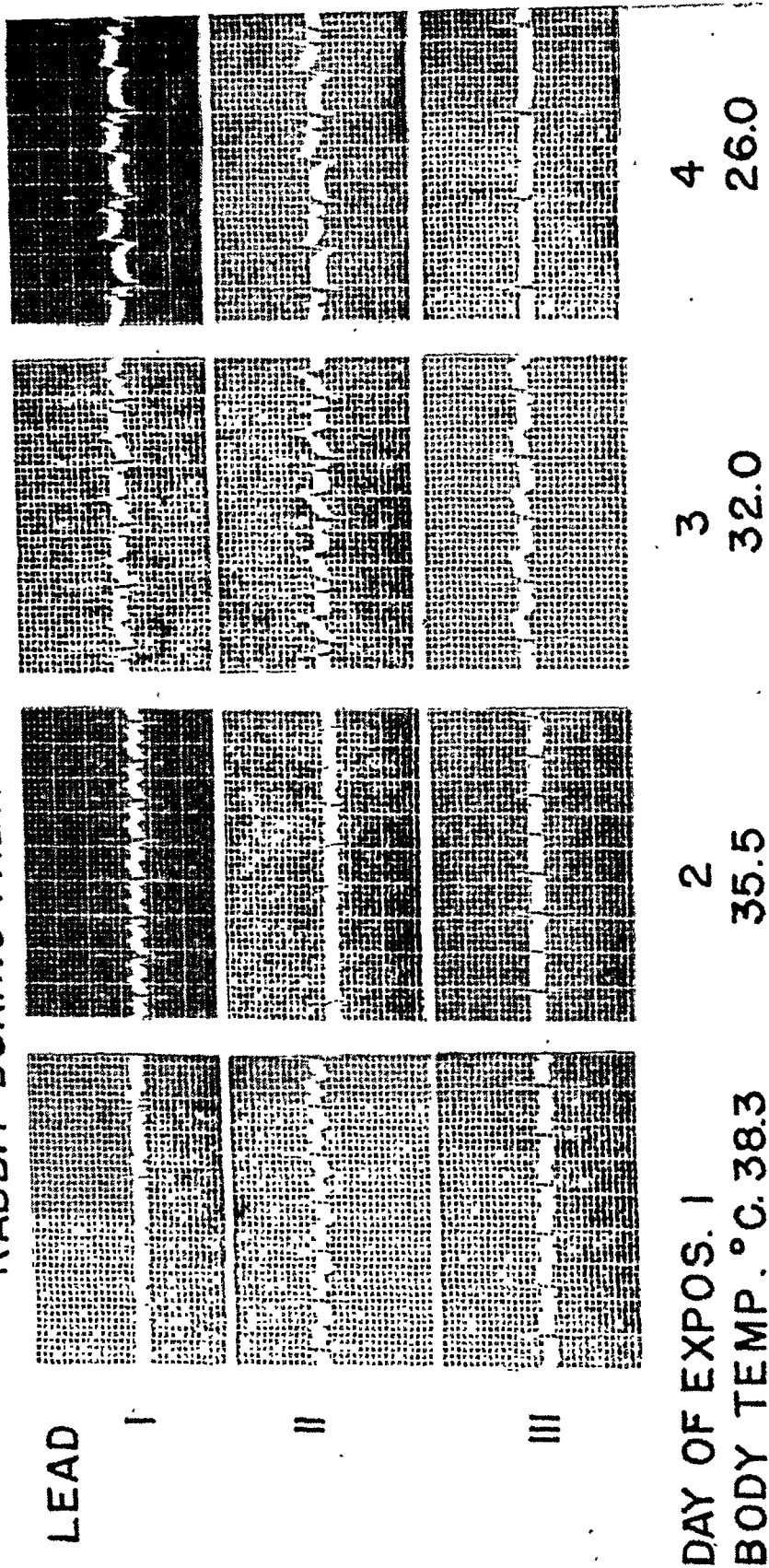


Fig. 1. Electrocardiograms of a rabbit during trenchfoot exposure with general loss of body temperature.

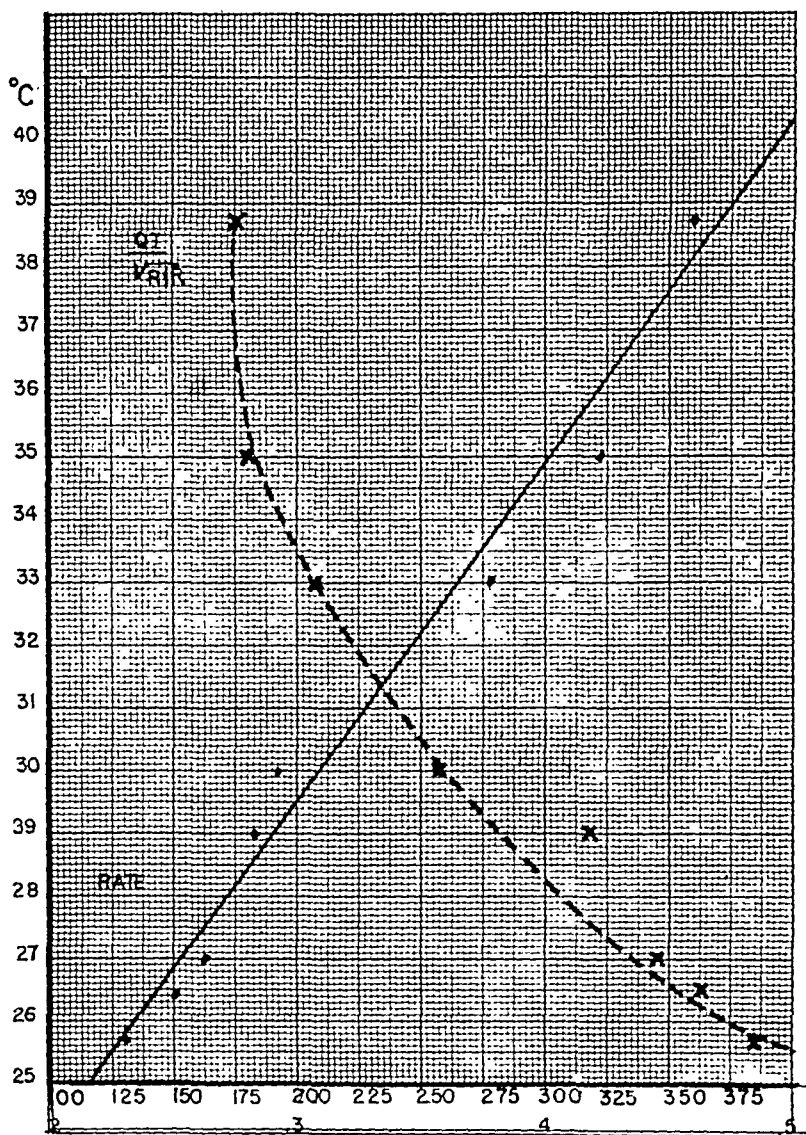


FIG. 3. Relation between body temperature, heart rate and electrical systole in a clipped rabbit exposed to an air temperature of  $-20^{\circ}\text{C}$ . Rewarming on electric heating pad.

slope of the curve permitted an exact prediction as to when heart standstill and death would occur and in those experiments which were carried to death under artificial respiration this prediction proved to be correct. The fact that artificial respiration at a constant rate did not influence the drop in heart rate proves that anoxemia does not have an influence on this relation. The P-R intervals and the QRS complexes became progressively longer in roughly a straight line relation to body temperature. The QT interval as evaluated by Bazett's formula showed changes which indicate a marked prolongation of systole during each cycle progressing with falling body temperature. The relation, although not linear, is a function of the temperature such that the systole is relatively more prolonged at lower temperatures (figure 3, table 2). These relations of prolongation of P-R

at 20° C. it is only 3 per cent (figure 4). This means that although the hemoglobin is fully saturated with oxygen it is unable to release it to the tissue. We may then be dealing with an anoxia without anoxemia. It is interesting to note that poikilothermic animals have a much higher oxygen dissociation at low temperatures than homoiothermic animals thus enabling them to supply oxygen to their tissues even at low body temperatures.

The possibility occurred to us that Cytochrome C may be able to help the transfer of the oxygen from the hemoglobin to the tissue. Six animals were therefore given 2 to 4 c.c. of Cytochrome C (Wyeth) after they were cooled to a body temperature of approximately 25° C. The electrocardiographic changes were not in the least improved by this treatment.

#### OXYGEN DISSOCIATION CURVES FOR HUMAN BLOOD

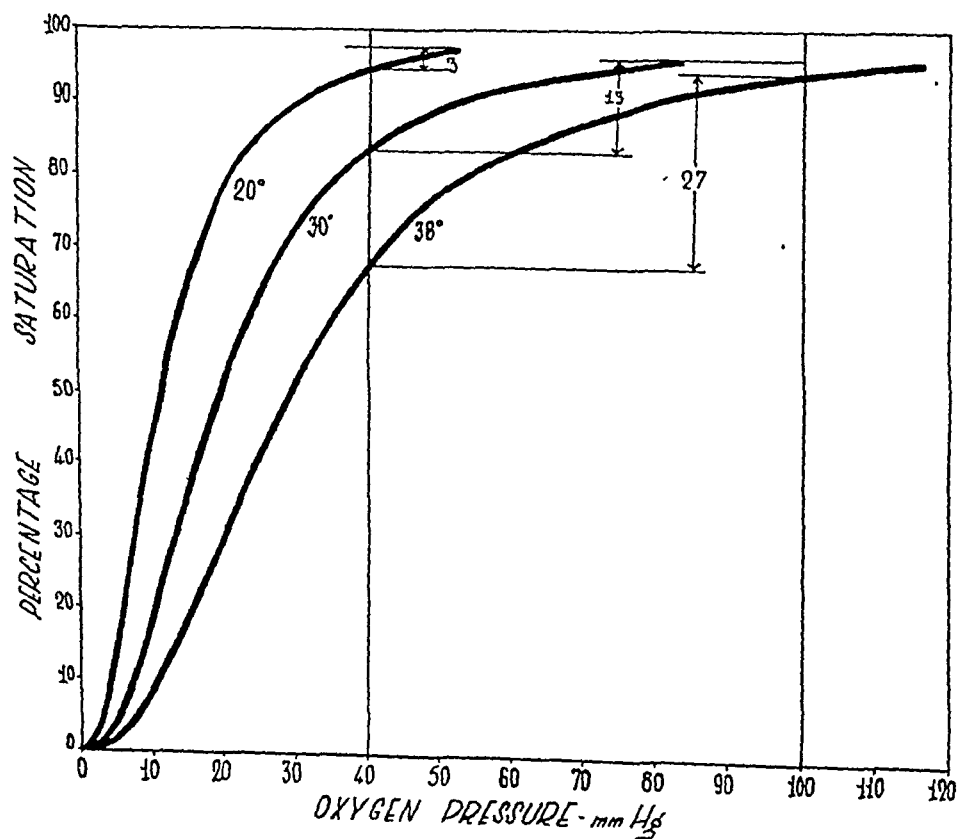


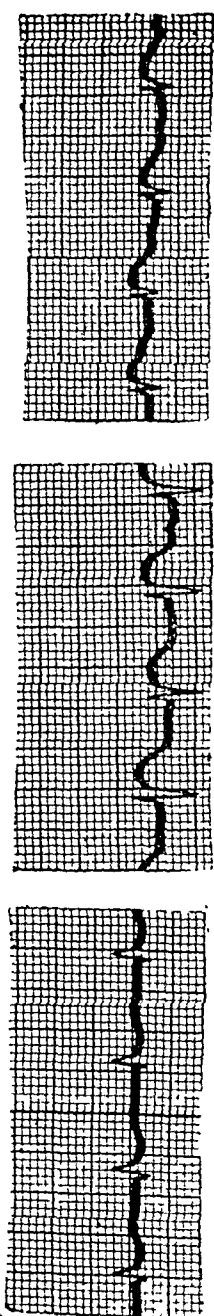
FIG. 4. Oxyhemoglobin dissociation curves for human blood at various temperatures.

We attempted to compensate for the lowered oxygen dissociation by increasing the amount of oxygen physically dissolved in the plasma independent of the hemoglobin. We calculated that this would require a 25 fold increase in the partial pressure of oxygen in the inspired air. This was accomplished by placing a severely cooled rabbit in a compression chamber containing 100 per cent oxygen at a pressure of 75 pounds per square inch.

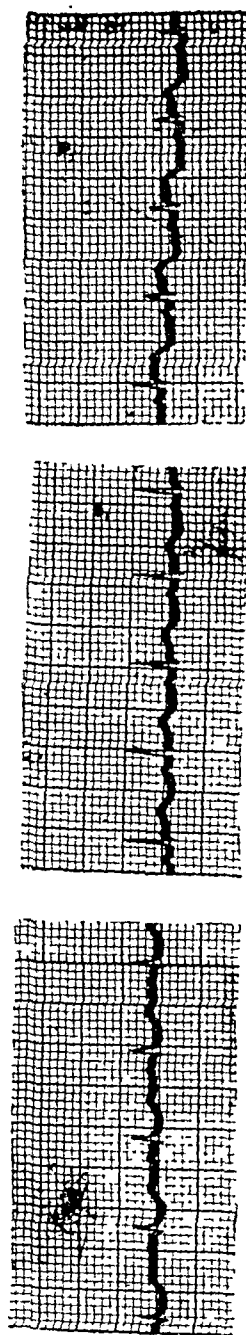
# EFFECT OF OXYGEN UNDER HIGH PRESSURE ON ANOXIA DUE TO HYPOTHERMIA

Body temp °C

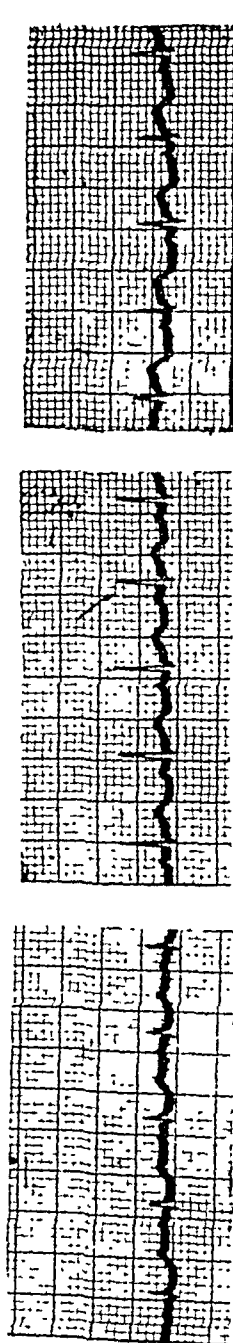
COOLED TO 28



4 min in PRESSURE  
CHAMBER AT 76 lbs/sq. in.



6 min in PRESSURE 27.5  
CHAMBER AT 76 lbs/sq. in.



R 836

FIG. 6. Electrocardiograms (limb leads) of a rabbit after hypothermia and before and after exposure to an atmosphere of 100 per cent oxygen under a pressure of 75 lbs. per sq. inch.

# EFFECT OF ACIDIFICATION ON ANOXIA DUE TO COLD (ART. RESPIRATION, PENTOBARBITAL SODIUM)

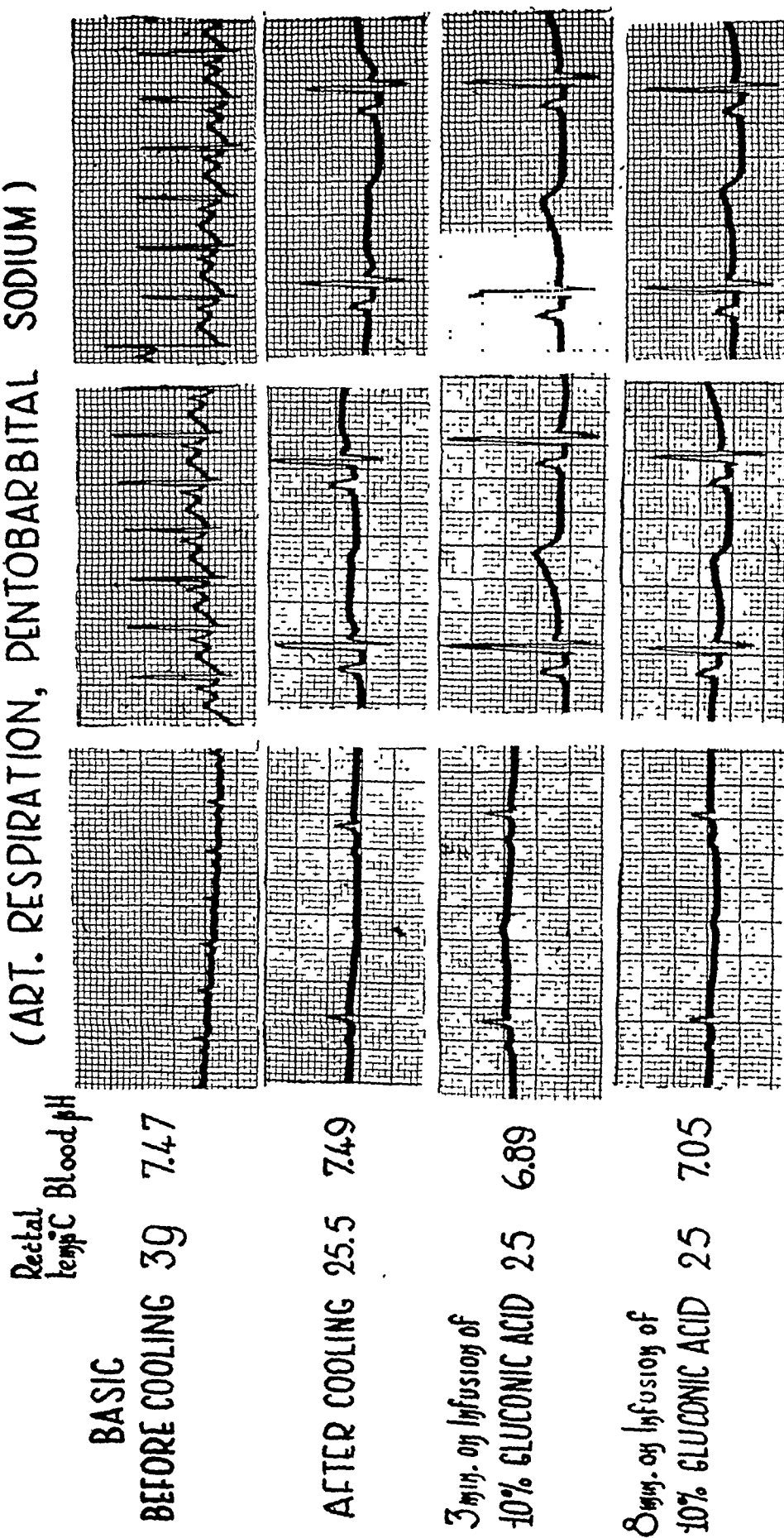


FIG. 8. Electrocardiograms of a clipped, anesthetized rabbit under artificial respiration exposed to an air temperature of  $-20^{\circ}\text{C}$ . After a severe hypothermia  $\text{NaH}_2\text{PO}_4$  is injected.

anoxia for they can be completely reversed by making oxygen available through acidification of the blood with subsequent improvement of the oxygen dissociation or by increasing the amount of oxygen physically dissolved in the plasma. It is therefore possible that the reported deaths subsequent to severe exposure to cold are due to longstanding anoxic damage of the heart muscle too early to be detected by present morphologic methods.

In patients recovering from hypothermia it may therefore be advisable to treat them for a short period of time as if they had myocardial infarctions.

### SUMMARY

1. The literature on the influence of hypothermia on cardiac rate, conduction and the myocardium is reviewed.

2. Rabbits suffering from slow or rapid lowering of body temperature show a reduction in heart rate directly proportional to the fall of body temperature.

3. The P-R interval and the QRS complex are also roughly proportional in their prolongation to the fall in body temperature.

4. The relative prolongation of electrical systole is not a linear function of body temperature. It becomes relatively more prolonged at lower body temperatures.

5. The very marked changes in the S-T segment and the T wave under such conditions show individual differences in extent and localization.

6. The changes in rate and conduction are exclusively the result of the direct effect of cold. The prolongation of electrical systole is partly the result of cold directly on the muscle fibers and partly the result of anoxia due to lowered oxygen dissociation. The T wave changes are exclusively the result of anoxia.

7. The anoxic nature of the S-T segment and T wave changes as well as part of the prolongation of electrical systole is proved by the fact that increasing the oxygen dissociation of the blood by acidification reverses them to normal. Increasing the amount of oxygen physically dissolved in the plasma also reverses these changes.

8. Acidification of the blood does not change the electrocardiogram of uncooled rabbits.

9. Anoxemia plays no rôle in the production of any of the changes seen in the heart with exposure to cold. We are dealing with anoxia without anoxemia.

### BIBLIOGRAPHY

1. WAYBURN, E.: Immersion hypothermia, *Arch. Int. Med.*, 1947, lxxix, 77.
2. UNGLEY, C. C.: Research and development of life saving equipment. Medical aspects of shipwreck. British Intelligence Objectives Sub-Committee Final Report No. 494, Item No. 24.
3. ALEXANDER, L.: The treatment of shock from prolonged exposure to cold, especially in water. Combined Intelligence Objectives Sub-Committee.
4. SMITH, L. W.: The use of cold in medicine, *Ann. Int. Med.*, 1942, xvii, 618.

# CORONARY OCCLUSION AND MYOCARDIAL INFARCTION ASSOCIATED WITH CHRONIC RHEUMATIC HEART DISEASE \*

By FRANCES E. GARDNER, *London, England*, and PAUL D. WHITE, *F.A.C.P., Boston, Massachusetts*

ALTHOUGH isolated cases have been reported (Kerr et al., 1925; Breitenecker, 1931), coronary artery obstruction has long been regarded as an uncommon complication in rheumatic heart disease. White and Jones (1928) found only one patient who had suffered a coronary thrombosis in 956 cases of rheumatic endocarditis. Among 99 patients dying with pure aortic stenosis Contratto and Levine (1937) reported four instances of coronary occlusion, and in 314 consecutive cases of simple mitral stenosis (Levine and Kauvar, 1941) coronary occlusion was diagnosed in only 10 instances (confirmed at autopsy in five). Rheumatic heart disease is found in less percentage still among patients with coronary heart disease. Only recently Cassidy (1946) reported that in 2000 cases of coronary heart disease he has not seen a single instance of concomitant chronic rheumatic endocarditis.

There seems no a priori reason why middle-aged and elderly patients with rheumatic heart disease should not develop coronary artery atherosclerosis as frequently as others without rheumatic stigmata. Indeed, since right and left ventricular hypertrophy commonly follow rheumatic valvular lesions, it might even be supposed that the latter condition would predispose to coronary insufficiency. Moreover, if, as Zeek (1932) and Karsner (1934) have claimed, acute rheumatic fever is attended by widespread lesions of the coronary arteries and predisposes to precocious coronary sclerosis, it might be assumed that patients with rheumatic heart disease would be unduly liable to coronary thrombosis and that this liability would become apparent at an earlier age than is usual in uncomplicated degenerative coronary disease. The reported figures suggest that coronary occlusion is infrequent in rheumatic heart disease; it is noteworthy, however, that with the exception of Levine's and Kauvar's five autopsied cases the figures are based on clinical diagnoses alone.

It is our belief that, in the absence of signs of gross valvular lesions, the presence of rheumatic heart disease may be overlooked in elderly patients and hence the real frequency of the association of this condition with coronary heart disease, if based on clinical records alone, may be underestimated. We have, therefore, made a study of necropsy material and compared the results with our more recent clinical records in order to check any discrepancy in our clinical findings. We also hoped to obtain a clearer picture of the relationship, if any, between rheumatic and coronary heart disease.

\* Received for publication June 3, 1948.

affected alone in five hearts and the mitral valves alone in four. Mitral stenosis was judged to be present in 13 cases and aortic stenosis in eight. Using White's criteria (1944) for the measurements of the valve circumferences we would consider only seven patients to have had clinically important mitral stenosis, that is, a circumference of the mitral orifice of less than 7.5 cm., and in no case was the aortic ring less than 5 cm. in circumference. Myocardial infarction was found in 25 hearts. In 12 the infarcts were recent, in eight they were of long standing, and in five there were both old and recent infarctions. In all but three cases the left ventricle bore the brunt of the infarctive process and anterior wall infarctions (19) were found with slightly greater frequency than posterior (15). Widespread atherosclerotic disease of the coronary arteries was found in all but one instance. In eight hearts no actual occlusion of the coronary artery could be demonstrated, but in nine two or more large vessels were thrombosed.

*Correlation of Clinical with Pathological Findings.* A correct ante-mortem diagnosis of combined rheumatic and coronary heart disease was made in only seven of the 32 patients. Coronary heart disease alone was diagnosed in 20 cases, rheumatic heart disease alone in four, and in one patient who died of a cerebral accident after a vaginal hysterectomy neither condition had been suspected during life. In only five cases was there failure to recognize the coronary heart disease, though in 10 the presence of recent myocardial infarction was unsuspected. Rheumatic heart disease was unrecognized in 21 of the 32 patients, and mitral stenosis was missed in three of the seven patients where definite postmortem evidence of considerable stenosis was present.

TABLE I

Showing (I) Age and Sex Distribution of Patients Dying with Uncomplicated Coronary Heart Disease, Uncomplicated Rheumatic Heart Disease, and Combined Rheumatic and Coronary Heart Disease in 6,000 Consecutive Autopsies at the M. G. H. and (II) Age and Sex Distribution in 57 Patients with Combined Rheumatic and Coronary Heart Disease in 10,000 Consecutive Cases Seen in the Private Practice of P. D. W.

Age	I Necropsy Series									II Clinical Series
	Uncomplicated Coronary Heart Disease			Uncomplicated Rheumatic Heart Disease			Rheumatic and Coronary Heart Disease			Rheumatic and Coronary Heart Disease
	All	M	F	All	M	F	All	M	F	
Under 40	11	10	1	122	61	61	0	0	0	0
40-49	34	30	4	69	36	33	2	2	0	2
50-59	115	90	25	88	49	39	12	6	6	30
60-69	179	128	51	75	45	30	13	5	8	16
70-79	119	79	40	41	24	17	2	0	2	9
80-89	23	13	10	9	5	4	3	2	1	0
Total 40 years and over	470	340	130	282	159	123	32	15	17	(M 40; F 17) 57



diastolic murmur with definite presystolic accentuation, and the diagnosis of rheumatic heart disease with slight aortic stenosis and regurgitation and slight mitral stenosis was made. Since that time the same murmurs have invariably been present, though often very careful auscultation has been necessary to detect them.

We now think it possible that a recurrent smoldering rheumatic carditis may have been partially responsible for the periods of ill health and left ventricular failure to which this patient was subject, but the hypertension and the myocardial infarction had been thought to be sufficient explanation for her condition until unequivocal evidence of valvular disease appeared. Had this complication been in mind, it is possible that a more diligent search might have revealed characteristic murmurs at an earlier date.

### DISCUSSION

The small number of cases with completely accurate antemortem diagnosis in our autopsy series demands comment. That rheumatic heart disease was unrecognized in as many as 21 of 32 cases suggests a low index of clinical suspicion. It is true that only in seven instances was there any considerable stenosis of the mitral valve, but three of these were unrecognized during life. It is also true that several patients were moribund when first examined and any signs of valvular disease which may have been present were obscured by tachycardia, gallop rhythm, or pulmonary edema consequent upon acute myocardial infarction, but in these, so far as we know, the diagnosis of rheumatic heart disease had not been made prior to their coronary illness. Moreover, it may be difficult to diagnose rheumatic heart disease with certainty in elderly patients. A history of rheumatic fever in youth is frequently lacking; it was obtained in only five of the undiagnosed cases. The presence of auricular fibrillation is of little assistance, for in this age group this arrhythmia may be due to a number of causes other than rheumatic heart disease with mitral stenosis. In our series it was found in only three of the patients with unsuspected rheumatic heart disease where adequate observation was possible during life, and in these either coronary or hypertensive heart disease was thought to be sufficient explanation. Nevertheless, there is a certain unawareness of the possibility of combined rheumatic and coronary heart disease. In several instances the significance of basal and apical systolic murmurs was underestimated, and in three patients although aortic valve disease was recognized during life it was attributed to atherosclerotic changes rather than to rheumatic heart disease.

Although the numbers in our autopsy and clinical series are small, it is clear that we are still overlooking chronic rheumatic endocarditis among patients with coronary heart disease, for in the clinical series only 2.0 per cent of the patients with the latter condition had recognized rheumatic heart disease in contrast to the 6 per cent in the autopsy series. It might be questioned whether or not unrecognized rheumatic heart disease has any significance in patients under observation for coronary insufficiency. Certainly unrecognized recent myocardial infarction has more serious conse-

## SUMMARY

1. In 6,000 consecutive autopsies there were 436 cases of rheumatic heart disease and 513 cases of coronary heart disease, 32 of which had both conditions (7 per cent of the rheumatics and 6 per cent of the coronary cases). Fifteen were male and 17 female.

2. In 10,000 consecutive clinical cases 1,346 were diagnosed as having rheumatic heart disease and 2,840 coronary heart disease, 57 of which had both conditions (4.2 per cent of the rheumatics and 2.0 per cent of the coronary cases). Forty were men, and 17 were women.

3. Aortic valve disease was found in 28 of the 32 fatal cases of combined coronary and rheumatic heart disease (87 per cent). It was present in only 69 per cent of the fatal cases of uncomplicated rheumatic heart disease. Mitral valve disease was found in 27 of the 32 (84 per cent).

4. A completely correct antemortem diagnosis was made in only seven of the 32 cases, although either rheumatic or coronary heart disease was diagnosed in 31 of the cases. The rheumatic heart disease was overlooked in 21 of the 32 patients.

5. Incomplete diagnosis was to some extent inevitable because of the moribund state of some of the patients when examined. To some extent it was probably also due to a common clinical unawareness that coronary and rheumatic heart disease may be associated.

6. The relatively low incidence of rheumatic heart disease among the coronary cases in the clinical series suggests that the former condition is still being overlooked in these patients.

7. Complete diagnosis is an important preliminary to satisfactory management. The value of careful auscultation in establishing the diagnosis of concomitant rheumatic heart disease is emphasized.

8. We have found no evidence to suggest that rheumatic heart disease has any influence on the development of coronary artery degeneration.

## BIBLIOGRAPHY

- BREITENECKER, L.: Ueber einen Fall von Aortitis rheumatica (Plötzlicher Tod eines 22 Jährigen Mädchens unter medikamentösem Vergiftungsvergacht), *Deutsch. Ztschr. f. d. ges. gerichtl. Med.*, 1931, xviii, 312.
- CASSIDY, M.: Coronary disease: Harveian Oration of 1946, *Lancet*, 1946, ii, 587.
- CONTRATTO, A. W., and LEVINE, S. A.: Aortic stenosis with special reference to angina pectoris and syncope, *Ann. Int. Med.*, 1937, x, 1636.
- KARSNER, H. T., and BAYLESS, F.: Coronary arteries in rheumatic fever, *Am. Heart Jr.*, 1934, ix, 557.
- KERR, W. J., LARKEY, S. V., and LARSEN, A. E.: Coronary occlusion and myocardial degeneration, *Calif. and West. Med.*, 1925, xxiii, 46.
- LEVINE, S. A., and KAUFMAN, A. J.: Association of angina pectoris or coronary thrombosis with mitral stenosis, *Jr. Mt. Sinai Hosp.*, 1942, viii, 754.
- WHITE, P. D.: Heart disease, 1944, The Macmillan Co., New York, pp. 580, 611, 624.
- WHITE, P. D., and JONES, T. D.: Heart disease and disorders in New England, *Am. Heart Jr.*, 1928, iii, 302.
- ZEEK, P.: Studies in atherosclerosis: atheroma and its sequelae in rheumatic heart disease, *Am. Jr. Med. Sci.*, 1932, clxxxiv, 356.

the following: (1) a relief of anginal pain which may be partial or complete, (2) an increase in the exercise tolerance so that walking and ordinary travelling is possible, (3) the ability to care for the daily needs, (4) the return to some gainful occupation.

In the study and surgical rehabilitation of these patients, we have not attempted to classify angina according to its etiology. We believe that it is a result of coronary artery insufficiency which in turn produces a myocardial ischemia. The rationale of surgery in this situation is an attempt to overcome the myocardial ischemia by the production of a collateral circulation as well as the production of a myocardial hyperemia.

There have been many surgical attempts to produce a collateral circulation to the myocardium. The term "collateral" is used here in a broad sense, meaning the establishment of a new circulation in part, or a new or more efficient use of the old circulation. The theoretical weakness of these procedures is that they do not eliminate or check the continuing coronary artery disease although, in a mechanical way, they do correct the effects of the disease. Because the disease process is not eliminated, the surgical procedures cannot be considered as curative measures.

The collateral circulation can be produced in a number of ways, using a variety of technics and would appear to be the logical method in the treatment of coronary artery disease. The attachment of some vascular tissue to the heart is one of the essential features of almost all of the surgical procedures. Until recently the likelihood of producing a myocardial hyperemia as a definite part of the treatment has been overlooked.

Many tissues have been used to provide a new or collateral blood supply. Among them are skeletal muscles, omentum, intrathoracic tissue, lung or mediastinal fat, and the pericardium. Grafting tissue on the myocardium produces a collateral circulation in two ways: (1) Intra-cardiac, by the formation of new collaterals or by stimulating an increase in the size and function of these collateral channels which are already present in the heart; (2) Extra-cardiac, by the formation of new channels from the grafted tissues to the myocardium. Thus, by this method, the insufficient coronary flow is partially compensated by increasing the amount of blood supplied to the myocardium.

In our various experimental attempts to produce a collateral circulation we found, in the animals that survived the operations, two factors which were present in all the different methods. These were: (1) The surgical trauma and inflammation produced by the operation itself, which resulted in myocardial hyperemia; (2) The production of adhesions between the pericardium and myocardium. This led us to use the pericardium as the tissue from which to establish a collateral circulation.

Under normal circumstances, the pericardium is thin and appears to be almost avascular. However, the blood supply is abundant. It receives branches from the aorta, from the internal mammary, from the esophageal, from the phrenic, from the bronchial, from the mediastinal, and from the

still be unanswered. The results are easy to see, although our explanation of how these results occurred, may be at fault.

Following the introduction of the talc powder, a definite inflammatory reaction occurs, involving all of the structures in the mediastinum, the pleura, the pericardium, the epicardium and the adjacent myocardium, the esophagus and the lungs. One of the characteristic features of this inflammatory reaction is the tremendous hyperemia which is produced within a few hours. A fever accompanies this mediastinal reaction, lasting from five to 15 days and gradually subsides. We feel that this hyperemia of the myocardium not only opens up the anastomosing channels between the coronary arteries which are already present, but it also stimulates the formation of new inter-coronary channels. Because of the hyperemia, more blood is carried to and is present in the myocardium (just the opposite of myocardial ischemia). This reaction, therefore, is two fold in that it causes a dilatation of the existing vessels with a more efficient supply and distribution to the myocardium, and it also stimulates the formation of new vessels in the myocardium.

As a result of the inefficient lymphatic supply of the pericardium and the large size of the powder particle, very little, if any of the powder, is removed from the pericardial sac. The greater part of the powder remains indefinitely within the pericardial sac, fixed in the adherent tissues. In some instances, it very likely forms talcum powder granulomas and, as such, may persist for many years. Lichtman et al.<sup>6</sup> have recently reported talcum powder granulomas which were present for 10 to 15 years. One of the characteristic features of any granuloma is the hyperemia and the presence of a great number of blood vessels. Again we emphasize the fact that this is exactly the opposite of the ischemic myocardium of coronary artery disease.

By means of animal experiments we were able to demonstrate the ability of the pericardium to furnish a collateral circulation sufficient to overcome the ischemia produced by a sudden, complete ligation of a main branch of the coronary artery, when adhesive pericarditis had been previously established with talc powder.<sup>7</sup>

## DISCUSSION

Many questions have been raised as to the disadvantage or possible dangers of adhesive pericarditis. Whether by such an operation for the relief of one disease, another condition might be produced, which in time, would become as serious as the original disease? Whether the presence of an adherent pericardium might interfere with the function of the heart, or make extra work for the heart, thereby resulting in hypertrophy? We believe these questions have been thoroughly and satisfactorily answered and that adhesive pericarditis, per se, in no way interferes with the function of the heart or adds to its work.

It is necessary, at this point, to emphasize the difference between constrictive pericarditis and adhesive pericarditis. The two terms are fre-

angina. This may depend upon subjective findings such as a distinct and clearly defined anginal syndrome, pain of characteristic nature and distribution with a definite relationship to effort. Or it may depend upon objective evidence of myocardial disease as revealed by the electrocardiogram, although this is occasionally absent. (2) The lack of improvement after fairly prolonged medical treatment. (3) An extreme degree of disability, corresponding to at least class 3 of The Heart Association Classification, necessitating greatly limited physical activities.

A previous coronary occlusion is not a contraindication; however, sufficient time must have elapsed to permit healing of the infarct. The two principal contraindications to operation are congestive failure and an active infarct. An attempt is made to rule out the presence of an active process by means of serial electrocardiograms, blood sedimentation rates and white blood cell counts. These three tests are performed each day for four or five days immediately preceding the operative day. If the electrocardiograms are not stable and the other two tests show an abnormal increase, the operation is postponed.

The pre- and postoperative care, and the postoperative course have been previously described in detail and will not be repeated here.<sup>8</sup>

### OPERATIVE TECHNIC

The details of the operation have been thoroughly described elsewhere and only the essential features will be mentioned here.<sup>8</sup> They consist of an incision over the fifth left costal cartilage. Approximately two inches of this cartilage are removed leaving the perichondrium. The pericardium is opened for a distance of two inches. Five to 10 minutes before the pericardium is opened the patient receives 5 c.c. of 2 per cent novocaine intravenously to desensitize the myocardium. After opening the pericardium the fluid is aspirated with a soft rubber catheter and the anterior surface of the heart is inspected and palpated for previous infarcts, adhesions and the condition of the descending branch of the left coronary artery. Approximately two drams (by volume) of dry sterile talc powder is spread over the anterior surface, the right and left and inferior borders of the heart. The powder is spread as evenly as possible so that the myocardium is white but the powder is not caked in one spot. The wound edges are protected from the powder by covering them with moist gauze. The pericardium is now loosely and incompletely closed with fine catgut and the soft tissues are closed in anatomical layers.

The novocaine is now used intravenously rather than by topical application on the myocardium. The powder (U.S.P. talc) is prepared by fractional sterilization on three different days preceding the operation and must be dry for easy application at the time of the operation. The operation can be easily performed in less than 30 minutes.

occlusion which developed after the operation and one from a rupture through an unhealed infarct which was discovered at the time of the operation. These cases illustrate the extreme degree to which most of our clinical material was handicapped. They also illustrate the difficulty experienced, in spite of our tests, in detecting the presence of an active or unhealed infarct just before operation. Four of the six hospital deaths were in patients who had unhealed and unrecognized infarcts at the time of operation.

TABLE I\*

	Number	Per Cent
Total number of operations	36	100
Hospital deaths	6	16
Late deaths up to seven years	5	14
Number of patients disappeared	2	6
Living at present time	23	64

\* Since the time this paper was sent for publication, 4 additional patients have been operated upon with no deaths and all with marked improvement.

As can be seen from table 1, there was a total of 36 operations. Excluding the six patients who died in the hospital and one patient who died three weeks after leaving the hospital, and the two patients who could not be followed, we have 27 patients. These patients have been observed from the time of the operation up to the present time or the time of their death. Four of these patients died from one year and five months to six years and 11 months after the operation. Twenty-three are still living and one is nine years after the operation.

TABLE II

## Clinical Results

27 patients observed from the time of operation up to nine years or the time of death

Degree of Improvement	Number	Per Cent
Poor	4	15
Moderate	4	15
Marked	19	70

The results shown in table 2 are based on the criteria which we mentioned earlier and are used to determine the degree of rehabilitation, although the greatest emphasis was placed on the relief of the anginal pain. Seventy per cent were markedly improved and another 15 per cent were moderately improved. According to their own estimates 85 per cent of the patients were more than 50 per cent improved. Eight patients considered themselves to be completely relieved and normal.

The four patients having poor results still have their anginal pain although there is a slight improvement in the exercise tolerance particularly after the use of nitroglycerine. Three of these patients have returned to their former or other gainful occupations. Considering the amount of pathology and the degree of incapacity we believe the results are excellent.

# PHLEBITIS AND THE DIAGNOSIS OF THROMBO- ANGIITIS OBLITERANS \*

By EDWARD A. EDWARDS, M.D., *Boston, Massachusetts*

## INTRODUCTION

THE making of an early diagnosis in thromboangiitis obliterans is highly desirable. This is true not only because of the serious nature of the malady but also because its progress will usually be arrested if the patient is forced to cease smoking.

At least one-fourth of patients with the disease show an early phlebitis of their veins. This has been known since Buerger described it as "migrating phlebitis,"<sup>1</sup> yet the clinician often misses the opportunity to utilize the presence of venous involvement to make an early diagnosis. This report will try to demonstrate that by careful scrutiny of patients with thrombophlebitis, and especially with the help of the biopsy, cases of thromboangiitis may be discovered, and often before there is appreciable involvement of the arteries.

The phlebitis is of interest in late cases as well, both as an aid in establishing an otherwise presumptive diagnosis and as a sign of activity of the disease.

## CHARACTERISTICS OF THE PHLEBITIS

1. *The patient is a young person who smokes.* Thromboangiitis obliterans is overwhelmingly a disease of young males. The disease starts in the twenties or thirties. The writer has seen only one patient (Case 5) in whom it began after the age of 40. The patient is invariably a tobacco smoker.<sup>2</sup> Cases in women are extremely rare.

2. *The phlebitis may appear as an idiopathic process or may have a precipitating cause.* Often the phlebitis is initiated by trauma, and the true diagnosis is suspected only through migration of the lesion or its excessively long duration.

3. *The superficial veins are always affected; the deep veins possibly so.* The saphenous vein is most commonly attacked. Involvement of a vessel on the dorsum of the foot, or in the toes, is quite characteristic of the process, since one does not see phlebitis of other causes originating here. Any portion of the superficial veins of either extremity may be implicated. Occasionally, the phlebitis is noted in the external jugular or its tributaries.

It is uncertain how often the deep veins are inflamed in the early stages of the disease to form a part of the migrating phlebitis. That deep phlebitis of small veins is a frequent part of the process is suggested by the oft-occur-

\* Received for publication March 12, 1949.

From the Department of Surgery, Tufts College Medical School.

Aided by a grant from the Charlton Research Fund, Tufts College Medical School.

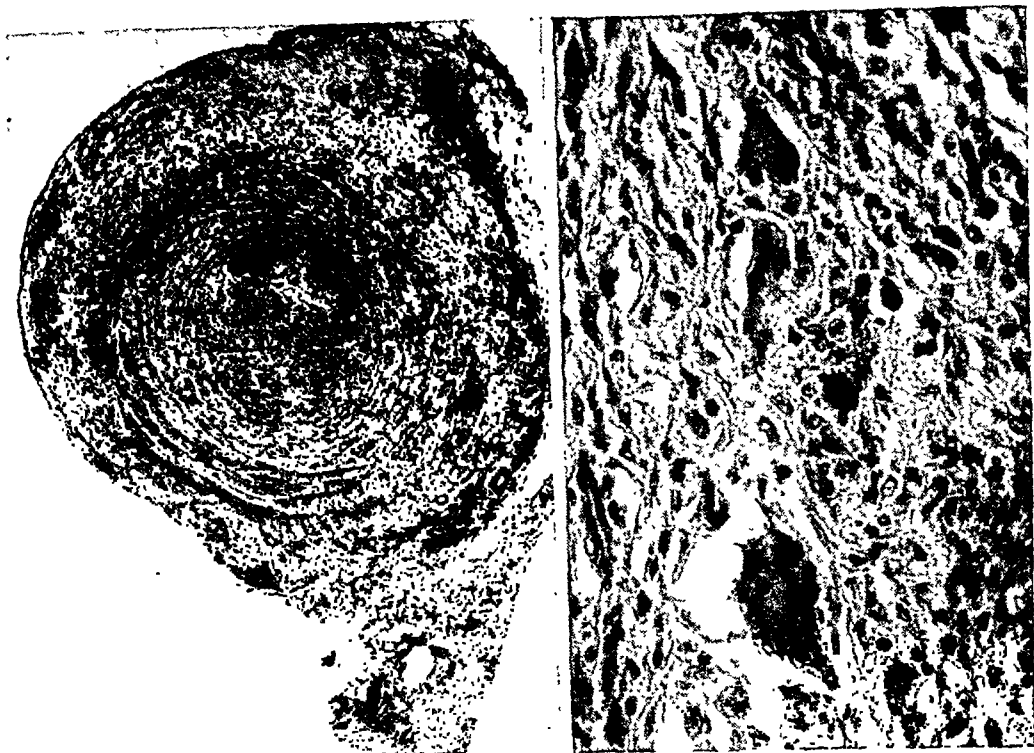


FIG. 1. The characteristic lesion of thromboangiitis obliterans.

*Left*, section of a saphenous vein involved in a migrating phlebitis. There is marked inflammation, with cellular infiltration throughout the entire vessel, extending to the perivascular tissues. Giant cells are present in the intraluminal granuloma. (Reprinted by permission from New Eng. Jr. Med., 1939, ccxxi, 251.)

*Right*, detail of the granuloma. (Reprinted by permission from Arch. Path., 1943, xxxv, 241.)

in the superficial veins during the migrating phlebitis. It should be sought for in vessels showing clinical signs of inflammation, and may be found in segments which have been inflamed for months or years.

Biopsy of an inflamed vein is therefore a diagnostic procedure of great value, and involves no special hazard. If the granuloma is found, and if the clinical picture is suggestive, the diagnosis is sure, even when an arterial lesion cannot be found. In the absence of the granuloma, a widespread inflammation of the vein extending to the perivenous tissue is suggestive of the diagnosis, but the author cannot say how much weight should be given to this finding.

#### MANAGEMENT

Data for the diagnosis of a case of phlebitis of uncertain origin will be obtained from a thorough history and physical examination. The laboratory will aid in uncovering blood dyscrasias. The clinical picture, occasionally aided by a biopsy, will establish the diagnosis of thromboangiitis obliterans. It is worth emphasizing that in the middle-aged patient a migrating phlebitis clinically resembling that of thromboangiitis obliterans has been found in association with visceral carcinoma, especially of the tail or body of the pancreas.<sup>5</sup> In these circumstances, the thrombophlebitis is even more



first seen, at 49, there were no pulsations below either popliteal level. The onset of symptoms after the age of 40, the absence of a history of phlebitis, and the slow course of his illness led to a probable diagnosis of arteriosclerosis.

At the age of 51, a phlebitis started at the right ankle and dorsum of the foot after a sunburn, and slowly ascended in the leg. Biopsy of the inflamed vein showed the typical granuloma and extensive inflammation of thromboangiitis obliterans, and established the true diagnosis.

*Case 6.* A 28-year-old laborer had suffered from gangrene of a toe after a crushing injury. The ulceration, amputation, and final healing occupied two years. After this, he was symptom-free for a year. He had not stopped smoking. One month prior to being seen, the right foot became painful and swollen. There was evidence of thrombosis of the popliteal artery, and simultaneously, a thrombosis of the veins of the dorsum of the foot, and of the leg. Biopsy of a vein showed the granuloma and other changes of thromboangiitis obliterans. The limb came to amputation.

In this patient, the appearance of thrombophlebitis coincided with activity of the disease in the arteries.

### CONCLUSIONS

The presence of a migrating phlebitis of uncertain origin, or of unusual course, may allow a diagnosis of thromboangiitis obliterans to be made before the arteries are involved. Both the clinical characteristics of the phlebitis and its appearance by biopsy are important in establishing the diagnosis.

In later cases, the phlebitis may aid in differentiating the arterial lesion from arteriosclerosis. The phlebitis may also serve as an index of activity of the disease in the arteries, or as a sign that the patient is continuing to smoke.

### BIBLIOGRAPHY

1. BUEGER, L.: The circulatory disturbances of the extremities, 1924, Saunders, Philadelphia.
2. SILBERT, S.: Etiology of thromboangiitis obliterans, Jr. Am. Med. Assoc., 1945, cxxix, 5-9.
3. KAHN, J. W.: Thrombophlebitis of the deep veins in thromboangiitis obliterans, Surg., Gynec. and Obst., 1946, lxxxiii, 449-452.
4. EDWARDS, J. E., and EDWARDS, E. A.: The venous valves in thromboangiitis obliterans, Arch. Path., 1943, xxxv, 242-252.
5. EDWARDS, E. A.: Migrating thrombophlebitis associated with carcinoma, New Eng. Jr. Med., 1949, ccxi, 1031-1035.

place in a simple fashion. There are four separate well-defined stages which characterize its development under BGE influence. Each of these stages which occur in succession, represents a complete step in the gradual formation of the "sickle."

It must be emphasized, however, that the BGE does not create any new figures. There is no essential difference in the appearance of the sickle cells produced by the BGE and those produced by anoxia in the sealed wet preparation. However, either because of the specificity of the BGE or its power, the successive changes in the red cells occur with a clarity in the details that are never observed in the simple sealed wet preparation.

The first stage is an enlargement and simultaneous thinning by stretching, of the disc. This picture is in some cases due to the uniformity, of extraordinary beauty.

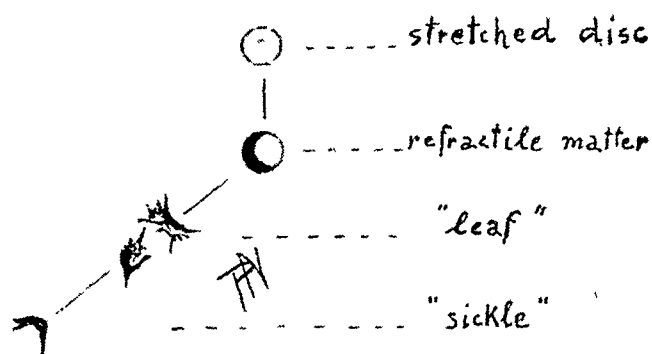


FIG. 1. The four regular stages in the sickle cell development under BGE influence.

The second stage is a striking change in the distribution and appearance of the hemoglobin. There are formed a highly refractile dense area or areas, while the remainder of the cell gets a smooth and paling appearance. Due to the rapidity of the change, stages one and two are often found together.

The third stage is a figure which for convenience because of its characteristic silhouette, may be called "leaf."

The fourth stage is the "sickle" which develops from the "leaf" after it has lost most of its prongs.

These four steps in the sickle cell development\* under BGE influence, more precisely in a feces-enzyme-broth, are shown schematically in figure 1.

Although the phenomenon has received its name from the "sickle"-shaped end stage, for reasons which will become later fully clear, the third stage or the "leaf" must be regarded the most significant of all. For the present, it is sufficient to state that the "leaf" is the first sign of actual cell destruction. While stages one and two are reversible, stage three the "leaf," is irreversible. It is of great clinical interest that the sickling process may in some cases exhaust itself with the third stage so that no further development to the

\* To be described and discussed more in detail in a subsequent paper.

and the BGE. Mere traces of plasma are capable of accomplishing this, as is shown in the following experiment.

Two BGE media, distinct with regard to the plasma content, one a usual feces-enzyme-broth (Schiff), the other a plasma-enzyme-broth (Neuda), were compared with regard to their respective action on the washed cells of a negress (P. G.) suffering from sickle cell disease. Result: the cells suspended in the feces-enzyme-broth, were at the end of 28 minutes transformed directly into "leaves" and "sickles," there was no sign of partition of the cells; the cells suspended in the plasma-enzyme-broth, however, revealed after 34 minutes widespread "block" partition with numerous "leaves" and "sickles" developing from the disconnected parts. Figures 3a, a photomicrograph, and 3b, a drawing, show block-partition and sickle formation together as obtained in this experiment.

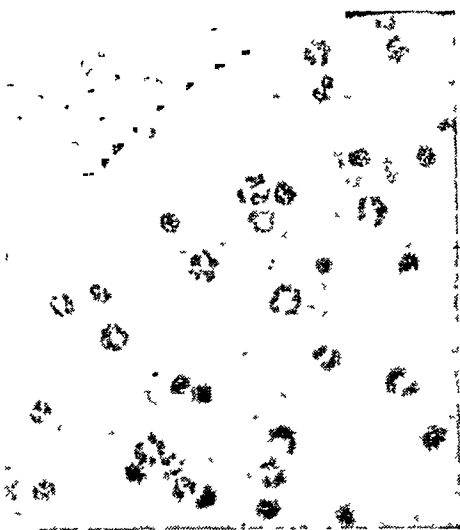


FIG. 3a.

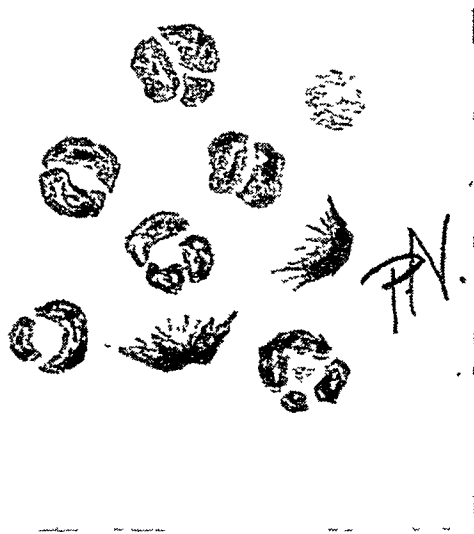


FIG. 3b.

Block-partition and sickle formation together, at left in a photomicrograph, at right in a drawing of selected figures (case F. G.).

This combined BGE-plasma-influence was demonstrated in repeated tests with a plasma-enzyme-broth. It was also reproduced with a feces-enzyme-broth if traces of plasma were added. The influence of the plasma seems to be of a general character and will require further investigation for its elucidation. In these experiments, always plasma of the same blood group was used.

The common occurrence of block-partition as an intermediary figure in sickle cell disease and as an idiopathic figure in both Caucasians and Negroes, in the latter in the absence of sickle cell disease, indicates that this figure very probably belongs to the same type of blood destruction as the "sickle." This is what I had previously termed "hemolysis of sickle cell type."

This concept is supported by the analysis of the 126 cases in this study. Block-partition was found in a significantly higher percentage in the blood

of blood destruction. They originate apparently by the loss of one "block" in the original circumference of the destroyed cell.

The traceable higher frequency in incidence of block-partition in the colored populace can be explained, at least partly, by the proved intimate connection which exists between this condition and the sickle cell disease. Of the above mentioned 11 Negroes exhibiting block-partition, six were afflicted with sickle cell disease. One might conclude that "hemolysis of sickle cell type" is more widespread in Negroes than in Caucasians. This may actually be so. However, the incidence of this type of hemolysis in Caucasians is not as rare as the above figures would indicate, since there are still other forms of this type of cell damage which can be met as often in Caucasians as in Negroes. A report on these other forms of "hemolysis of sickle cell type" will appear elsewhere.

Of a special interest will be the question, in which diseases can block-partition be expected? On the grounds of the evidence at our disposal, the following can be said. Block-partition tendency of red cells, as revealed by the use of the BGE, is a sign of an inherent liability, called sensitivity. It has, apparently, the same significance as the sickling tendency, though, as a disease, it is of a minor order. As in sickle cell disease, it is frequently found combined with anemia. Unlike sickle cell disease, however, it is not restricted to Negroes but occurs also in Caucasians. In the Negro, the phenomenon is clearly observable only in the absence of the sickling condition, since in its presence, the several blocks rapidly undergo further change to sickles.

The following are the clinical diagnoses in the cases in which block-partition has so far been found: liver disease, especially cirrhosis of the liver, Hodgkin's disease, a malignant ovarian cyst, endocrine disturbances, anemias of undetermined origin and sickle cell disease. Most of the information hitherto obtained on this curious condition, we owe to the sickle cell disease. This makes sickle cell disease a most important object of study for the further elucidation of the mechanism acting in "hemolysis of sickle cell type."

#### BIBLIOGRAPHY

1. NEUDA, P. M.: Red blood cell sensitivity to the blood-group-enzyme, *Science*, 1947 cvi, 296-297.
2. NEUDA, P. M., and ROSEN, M. S.: Preliminary report on a rapid method for diagnosing sickle cell disease, *Jr. Lab. and Clin. Med.*, 1945, xxx, 456-458.

riations can be defined and before it becomes possible to lay down the boundaries between normal and pathological.

### THE INSTRUMENT AND TECHNIC

The electrokymograph<sup>8,9</sup> was specifically designed as an attachment for use with the roentgenoscope and electrocardiograph. When these three units are utilized together, for the purposes of electrokymography, the basic function of each is as follows; the roentgenoscope provides the means for observing the cardiovascular silhouette of a subject and for positioning the electrokymographic pick-up unit over a selected area; the electrokymograph converts the motions and density changes of such selected points to corresponding current variations; and the electrocardiographic galvanometer records these variations on moving bromide paper (an electrokymogram). A carotid sphygmogram is simultaneously recorded for timing and orientation purposes.

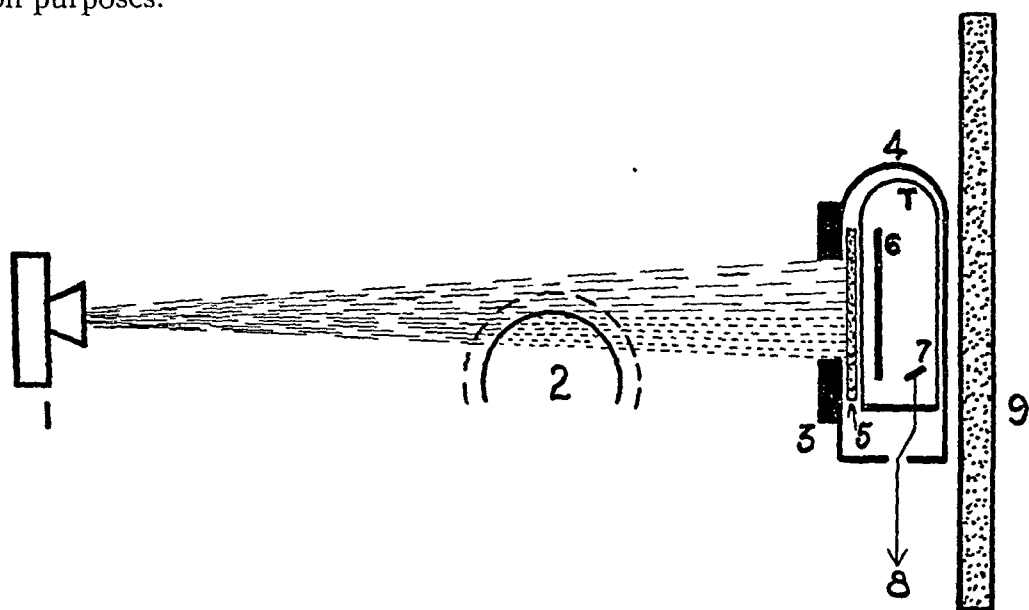


FIG. 1. Schematic illustration demonstrating principles of electrokymograph.

1. Source of roentgen-ray.
2. Heart in systole and diastole.
3. Limiting lead aperture.
4. Copper housing.
5. Small fluorescent screen.
6. Light sensitive surface of photo-multiplier tube (T).
7. Current collecting anode.
8. Connection to galvanometer.
9. Large fluoroscopic screen for general observation.

The electrokymograph consists principally of a roentgen-ray sensitive pick-up unit and its power supply. As shown in figure 1, the pick-up unit is made up of a lead diaphragm (3) with an aperture 5 by 20 mm., which serves to frame or limit the area to be recorded. Behind the diaphragm is placed a piece of fluorescent screen (5) with its light emitting surface close

amed are viewed through the fluoroscopic screen and the photo-tube mounting is swung into position, automatically centering the tube in the central beam of the x-ray. By manipulation of the fluoroscopic screen and rotation of the tube, the aperture of the pick-up unit is aligned so its long axis lies parallel to the direction of motion of the part to be studied (figure 2).

As soon as satisfactory alignment is accomplished, the technician introduces the signal into the galvanometer of the ECG by turning the "volume control" of the electrokymograph up slowly. The amplitude of the galvanometer excursions is controlled by this "volume control." The carotid-pulse shadow is again checked. When amplitude and alignment are satisfactory the patient is requested to "stop breathing" in the mid-phase of normal respiration and the ECG camera is started.

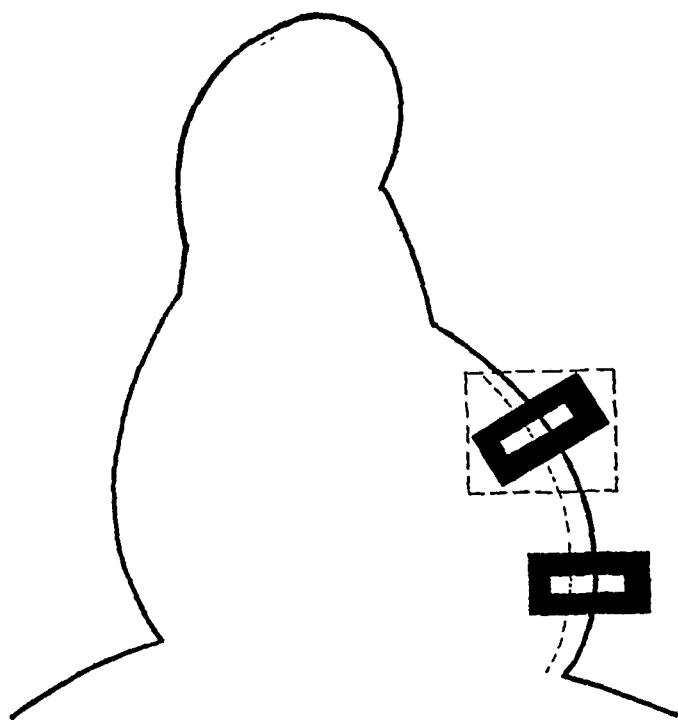


FIG. 2. Illustrating application of aperture of pick-up device over two points on cardiac silhouette. Note long axis parallel to direction of motion of borders, i.e. perpendicular to border. Moving shadow remains within aperture. After proper alignment of pick-up device, roentgen beam is coned by roentgenoscopic shutters (dashed square).

While no standard patient positions or views have been established for "routine" electrokymographic examination of the heart, the following segments of the cardiovascular silhouette have been examined in most instances: (1) Posterior-anterior projection; left ventricle (lower, middle, and upper), pulmonary artery, aortic knob, right atrium. (2) Right-anterior-oblique projection; left ventricle (lower and middle), pulmonary artery (when not obtained in posterior-anterior projection) and dorsally the areas of the right and left atria. (3) Left anterior-oblique projection; left ventricle (lower and middle), left atrium, ascending aorta, right ventricle.

equal to the cycle length in millimeters which gives a record with good characteristics for reading. The amount of motion at two points can be compared by taking records with the identical setting of the volume control. This gives an approximation of the relative amount of motion but the curves do not represent quantitatively the amount of movement. When recording from one point of the silhouette, variations in amplitude at a constant volume setting are significant. Another point to be remembered is that the instrument registers only that component of border movement which occurs at an angle to the axis of the central x-ray beam. When the movement is at a right angle, the greatest amplitude will be recorded. Movements in the same axis as the beam register only when they are accompanied by density changes of the part. These density and movement changes may then merge with or neutralize one another and thus alter the amplitude of the EKY.

The timing of the curves can be accurately determined. Time lines on the record are the same as for electrocardiography, i.e. each small space  $\approx 0.04$  sec. We believe the records can be read with an accuracy of  $\pm 0.01$  sec.

Many observations presented here substantiate and some differ from those made previously with the roentgenkymograph and other instruments. No attempt will be made to give individual credit to the many workers who contributed the remarkable fund of basic data on which we have drawn freely.

*The Ventricular EKY.* The left and right ventricular electrokymograms have basically similar configurations, though they may differ in detail. Each cycle consists of a major descending limb due essentially to the medial movement of the ventricular border during systole, and an ascending limb associated with lateral movement of the wall in diastole. Superimposed upon these two basic limbs are peaks, plateaus, and other variants. The records are surprisingly similar to volumetric curves of the ventricle obtained by direct cardiometer methods in animal experimentation.<sup>21</sup> Though they reflect volumetric changes to a remarkable degree, they also show effects from pendulum movement, rotation and shape changes of the heart.

The interpretation of the EKY from the carotid sphygmogram has been previously described.<sup>10</sup> The onset of the major ascending limb and the cleft of the incisura on the carotid curve are identified. Projection from these points to the EKY helps to identify the onset of ventricular ejection and the onset of isometric relaxation respectively. In many records the onset of the descending limb of the incisura is well defined and identifies the beginning of protodiastole; in some, ventricular isometric contraction is registered on the pulse wave. Starting from these points, the application of known facts concerning the phases of the cardiac cycle permits completion of the analysis.

When studying a right ventricular record, it is best compared with another right heart event, the pulmonary artery EKY. Since these are not simultaneously recorded, the carotid sphygmogram is used as a common time reference curve. A convenient method is to make a tracing on trans-

figures 3-D and E. The terminal portion of the ejection wave slopes more gradually and its end point is not definite in all curves. It is of interest to note that Wiggers<sup>21</sup> has observed a peak similar to that marked "x" in volumetric curves, which he called an "accidental" wave. In our records it appears to represent a shift in balance between positional and volumetric factors affecting border movement.

*Protodiastolic Phase (3-4):* This is the least clearly demarcated phase of the cardiac cycle on an EKY. It is approximately 0.04 sec. in duration and is a slightly concave descending segment. Its onset usually merges smoothly

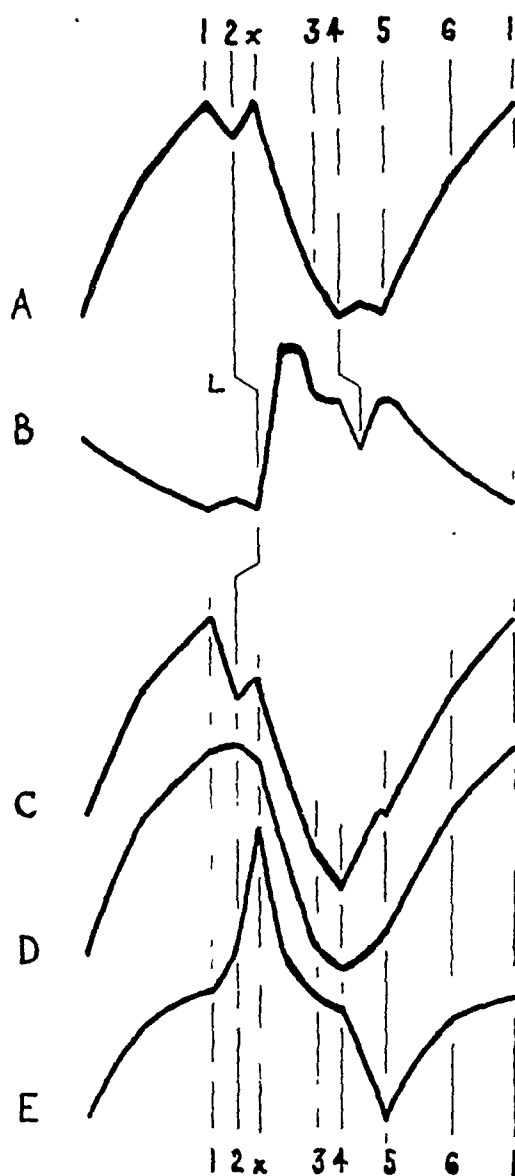


FIG. 3. Schematic drawing illustrating method of interpretation.

A, C, D, E—Variations of left ventricular electrokymograms, normal subjects. B—Carotid sphygmogram. L—Correction factor for lag of carotid recording system and pulse wave transmission time (see text). Vertical lines indicate phases of cardiac cycle.



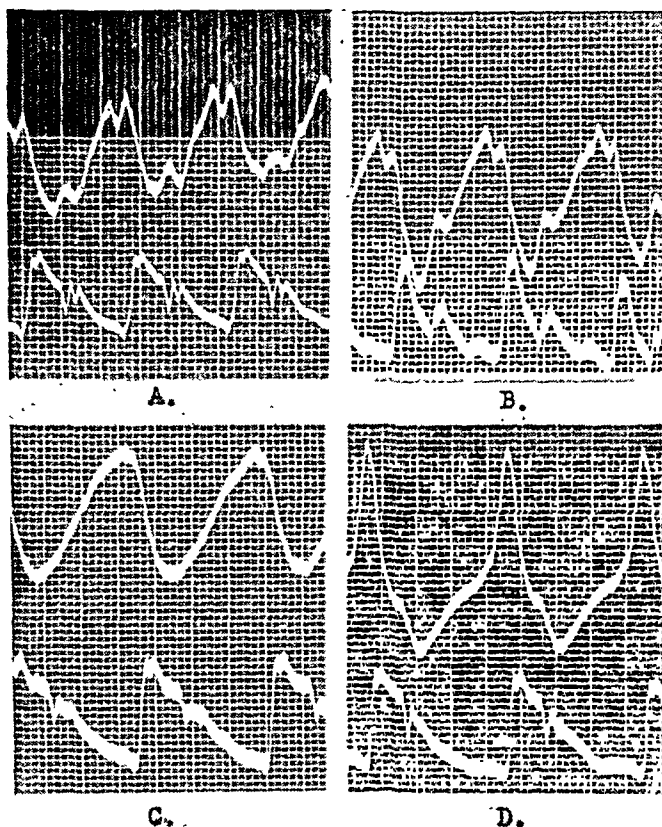


FIG. 4. Left ventricular electrokymograms showing variations in normal subjects.

In this, and subsequent illustrations, the upper curve is the EKY and the lower curve is the carotid sphygmogram.

A—PA projection, left lower border. B—Same projection, middle left border. C—LAO ( $20^\circ$ ), middle left border. D—LAO ( $60^\circ$ ), lower left border.

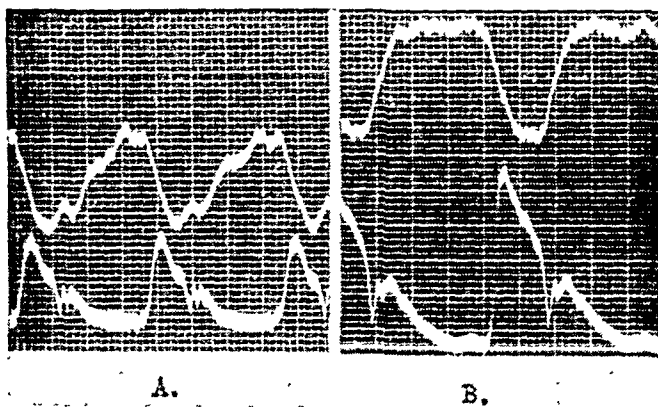


FIG. 5. A—EKY, middle left border, left ventricle (PA). Subject standing.  
B—Same with subject recumbent.

tomical relationship of the heart within the thorax, the slower heart rate and the increased ventricular filling which occur in the recumbent position. It has been noted that at rapid heart rates the ventricular curves may assume a more spiked contour.

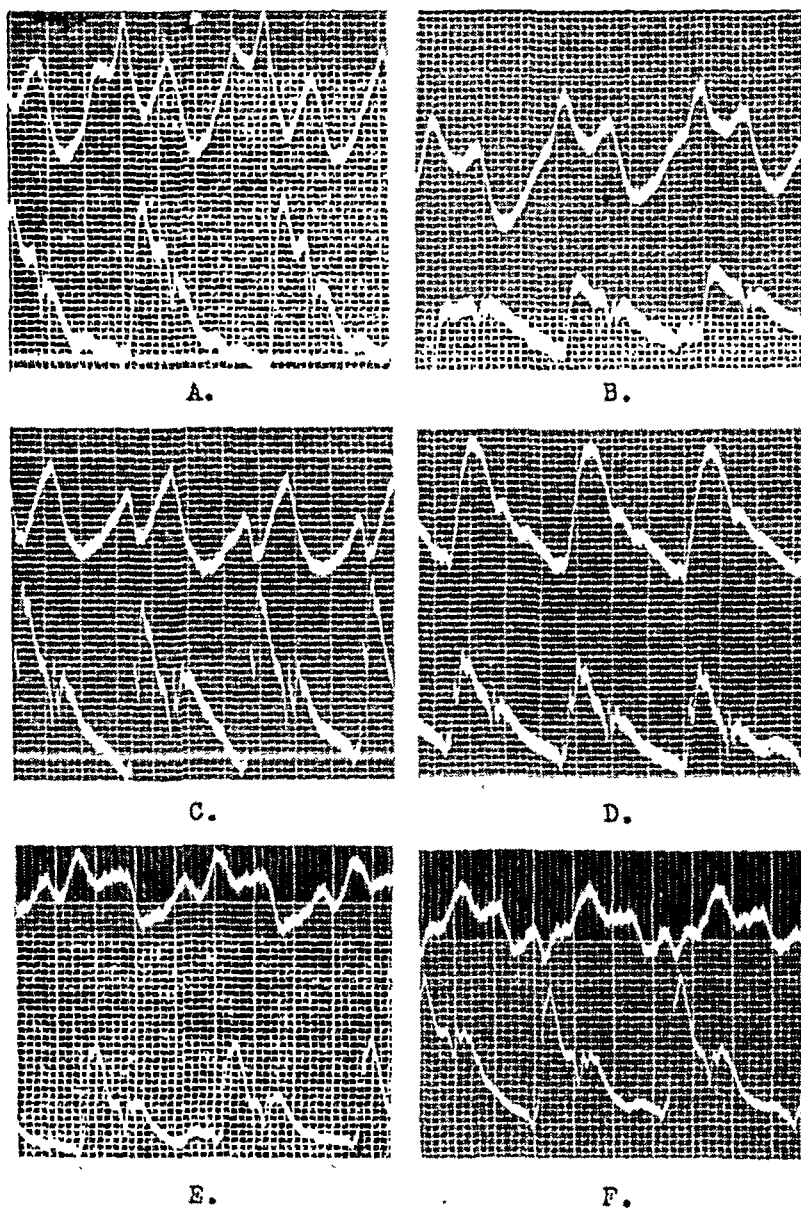


FIG. 7. Atrial electrokymograms illustrating variations in normal subjects. A, B, C—Right atrium, PA projection. D—Pulmonary artery EKY, subject C, for correlation. E, F—Left atrium, RAO and LAO respectively.

arteries may dominate the curve. The effect of these and other physiological factors may vary from patient to patient, on the right and left atrium, or on different segments of the same atrium. For example, a recording from the right atrium close to the cardio-phrenic angle, may show predominately ventricular type movements; near the middle of this chamber silhouette, the ventricular effects are less marked and more evidence of intrinsic atrial activity may be seen; along the upper segment, the movements of the ascending aorta and/or superior vena cava may modify the curve. These varying influences may produce changes in contour of the record which mask or

dominant factor and produces an outward movement despite the fact that the ventricle is still getting smaller. The V or L-shaped complex, 3-5, is quite consistently present and is often the largest complex of the right atrial EKY.

5-6: The third negative limb begins with the closure of the semi-lunar valves at 5 and ends with the opening of the a-v valves at 6. This movement is believed due to a positional shift of the heart as a whole. This can be shown in some cases by comparing movement of right and left heart borders. The depth of this limb varies, but it is clearly present in most records. Its duration is the same as that of the isometric ventricular relaxation phase as measured on the ventricular EKY. In some instances the complexes from 4 to 1 bear a different time relationship to the incisura of the arterial curves so that the semi-lunar valves appear to close between 4 and 5, and the a-v valves open at point 5. In such cases, the identification and interpretation of these complexes varies from that of the usual curve just described.

6-1: The third and final limb is correlated with the onset of ventricular filling. It might be expected that the atrial wall would move inward as blood passes from atrium to ventricle. During this period, however, the atrium rides outward on the expanding ventricle and apparently the column of blood in atrium and vein moves "en masse" so that very little intrinsic movement of the atrial wall occurs until its systole begins.

Right atrial curves were easily obtained in most subjects at approximately the middle of the right lower arc of the heart, with the subject erect and in the PA projection. Occasionally the right ventricle formed this segment of the silhouette. In the recumbent position, a predominately arterial or ventricular type wave was usually seen in this area.

The carotid sphygmogram is used directly to aid in the interpretation of the left atrial EKY. Referring to figure 6 and figure 7F, the movements of the left atrium between points 1 and 4 are similar to the movements of the right atrium. Between points 4 and 1, the curves usually differ, in that on the left atrium the semi-lunar valves appear to close between 4 and 5, while the a-v valves open at point 5. Phillips,\* and Luisada,<sup>19</sup> using the stethogram for orientation, reached a similar interpretation. In our experience it has been hard to obtain "pure" left atrial electrokymograms in normal subjects. It is difficult to be certain that this chamber is in silhouette and to visualize it free from adjacent structures in the various oblique projections. Even when the silhouette seems well visualized, the curves obtained often show predominantly ventricular, arterial or "mixed" characteristics.

In summary, it is emphasized that factors affecting atrial border movement are quite complex and at the moment we feel much as F. Roberts,<sup>24</sup> that the atriae, to a great extent, are passengers in the movements of the ventricles, making it difficult to distinguish between active and passive atrial movement.

\* Personal communication from Dr. Edward Phillips, Peter Bent Brigham Hospital, Boston, Massachusetts.

ceeds, a descending limb of lesser slope is inscribed. The end of the ventricular ejection phase is marked by a break in contour, or an incisura on the descending limb though not as definitely as on the carotid sphygmogram. The protodiastolic phase of ventricular activity is also not always clearly defined. The onset of ventricular diastole (isometric relaxation) is marked by a small upright wave which gives way to a gradually falling slope. This may be smooth in its descent or may show irregular undulations and peaks.

Electrokymograms from the aortic knob generally show an abrupt, steep, rising limb, a peaked contour, an "incisura" at a high level above the baseline, and a descending limb of lesser slope. In comparison with this, the pulmonary artery curves tend to show rising and falling limbs of more equal slope, a more rounded contour and "incisura" falling closer to the baseline. The electrokymograms of the ascending aorta are variable in appearance and in many instances show a large secondary wave after the incisura, figure 8E. This appears related to superior vena cava activity and probably represents an "impure" curve with both ascending aorta and superior vena cava in the recording aperture. Variations from these generalities are common so that it is not possible to identify a curve as pulmonary artery, ascending aorta, or aortic knob from its appearance alone. From rough comparisons, aortic curves appear of greater amplitude than pulmonary artery records, though standardization of height is not possible at present.

The technic of obtaining these records varies with the individual patient. In normal young adults it is easy to record the aortic knob movement in the posterior-anterior projection. Occasionally the knob may be inconspicuous and a slight degree of rotation may be needed to bring it out. The pulmonary artery tracings are usually obtained in the posterior-anterior projection, though at times it is necessary to rotate the subject into the right anterior oblique position. This is especially true in subjects with a transverse type heart. Electro-kymograms of the ascending aorta are taken close to the point of origin of the vessel and are most easily obtained with the subject in the LAO position. The optimum degree of rotation varies. As indicated before, the right border of the ascending aorta cannot always be thrown into silhouette free from the superior vena cava and the spine shadows. We have had difficulty in visualizing and recording the movement of the descending aorta below the aortic knob. Among subjects over 60 years of age, satisfactory arterial curves have not been obtained as easily as in younger subjects. A dilated or tortuous descending aorta or enlarged left ventricle, for example, may interfere with visualization of the pulmonary artery. Where, as in older subjects, the descending aorta forms a distinctly visible arc to the left of the spine its movements can usually be recorded. For movement to be recorded in this area, it appears that (a) the density of the vessel must be increased so as to give contrast with surrounding structures; (b) the vessel must be curved enough so that the passage of the pulse wave can produce a positional shift. Our work so far leads to the belief

*Column II:* The AKc measurement indicates the difference in the time of arrival of the pulse wave at the aortic knob and the carotid artery. It varies from  $+0.01$  sec. to  $-0.01$  sec., i.e. the onset of "ejection" on the aortic knob EKY may coincide with, or may precede or follow that on the carotid sphygmogram by as much as 0.01 sec. This variation can be explained by (1) differences in the distance from the left ventricle to the two points of recording; (2) differences in rate of pulse wave transmission from the aorta to the points of recording. A preliminary study of a large group of older men, most of whom had some degree of aortic arteriosclerosis with elongation and tortuosity, has shown a significant number of subjects in whom the aortic knob ejection point occurs as much as 0.05 sec. after the carotid ejection point.

*Column III:* AAc to AKc difference. This measurement indicates the time for transmission of the pulse wave from the ascending aorta to the aortic knob. It varied from 0.00 to 0.03 sec. (average 0.014 sec.). Again the 0.00 readings probably represent values between that figure and 0.01 sec. This value is prolonged in many older subjects.

In the living subject the distance from the point of recording on the ascending aorta to that point visualized as the "aortic knob" is variable. It can be estimated at 8 to 10 cm. from measurements given in anatomy text books.<sup>25</sup> Assuming that AAc to AKc times of 0.00 are actually 0.01 sec., the transmission time from the ascending aorta to the aortic knob becomes 0.01 to 0.03 sec. Then the pulse wave transmission rates in the aorta would be from 3 to 10 meters per second. This closely approximates prior estimates.<sup>26</sup>

*Column IV:* The PAc measurement indicates the difference in the time of onset of the ejection waves on the pulmonary artery EKY and that on the carotid sphygmogram. It serves to compare right and left heart events. It varied from  $+0.03$  to  $-0.01$  sec., i.e. pulmonary artery ejection might precede carotid ejection by as much as 0.03 sec., or follow it by as much as 0.01 sec. The range of the PAc measurement is sufficiently narrow and constant that unusual variations can be considered as indicative of abnormal degrees of ventricular asynchronism. In a large group of normal adults all measurements were between  $+0.03$  and  $-0.01$ . In 15 of 16 patients with bundle-branch block, measurements were significantly outside this range (LBBB 0.04 to 0.07 and RBBB  $-0.04$  to  $-0.05$  sec.).<sup>17</sup> Since this previous communication, we have examined a group of subjects over age 60, and to date their PAc measurements have corresponded to those of the younger age group except in two of 30 cases. One of the exceptions had a dilated descending aorta which may have been superimposed on the pulmonary artery.

*Column V:* PAc to AAc difference. This measurement can be used to determine the actual degree of asynchronism of ejection from right and left ventricles.<sup>17</sup> In normal subjects it was found that the PAc to AAc difference equals  $+0.03$  to  $-0.03$  sec., i.e. the ejection on the pulmonary artery EKY

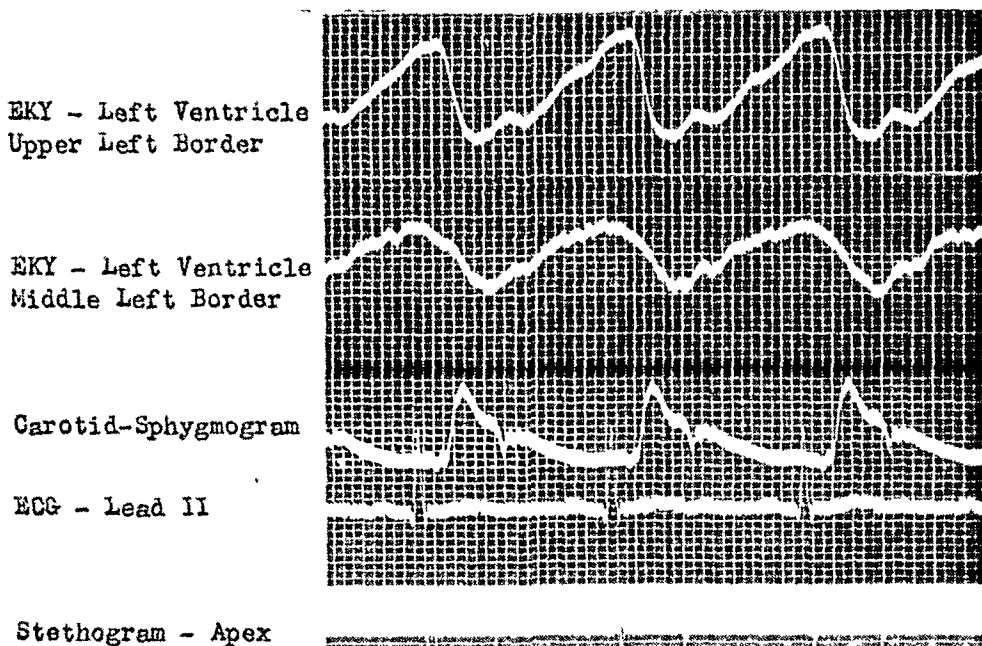


FIG. 10. Sample of simultaneous recording of multiple events.

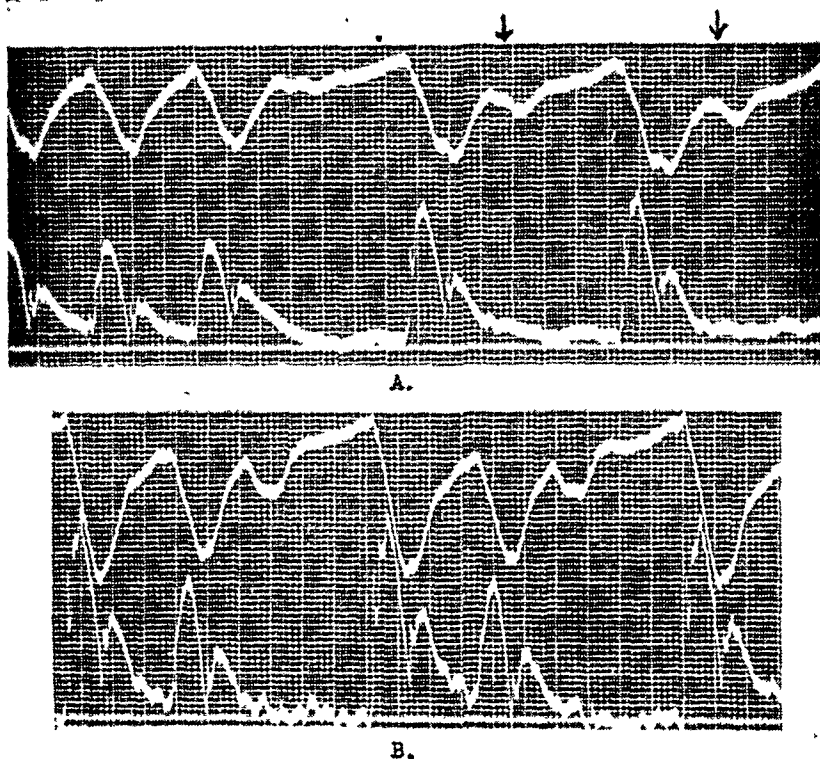


FIG. 11. Ventricular premature contractions.

Noted clinically and on ECG of subject with no other sign of heart disease. A—Lower left ventricle (PA). Normal rhythm changing to bigeminal. Arrow marks premature contraction which bulges, but fails to open semi-lunar valves. B—Period of trigeminal rhythm, same subject.

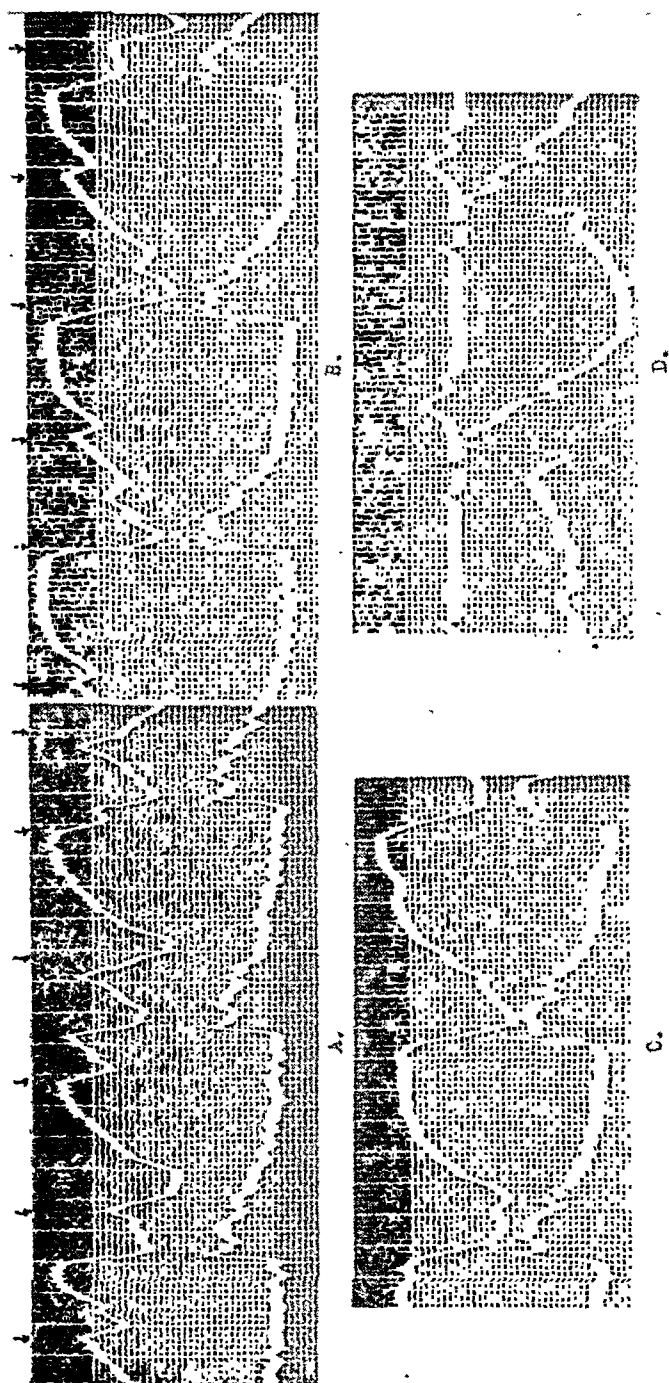
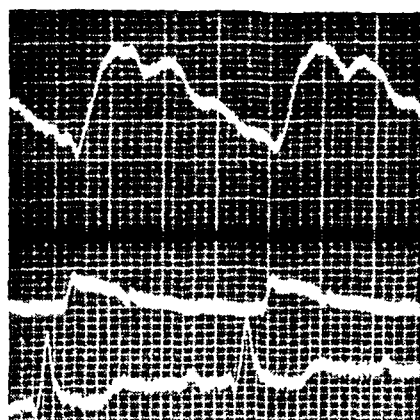
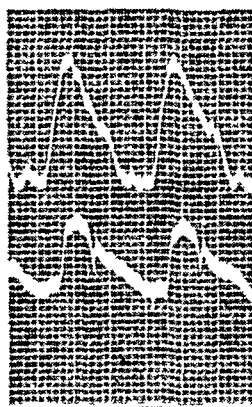


FIG. 13. Complete atrio-ventricular dissociation in subject with calcification annulus fibrosis, etiology unknown. No other signs of cardiovascular disease.

A—Left atrium (RAO). Recurrent descending limbs (arrow) associated with atrial contraction. Effect of ventricular systole evident at about one-half rate of atrium. B—Right atrium (PA). C—Middle left ventricle (PA). Large complexes associated with slow rate and prolonged diastole. D—Electrocardiogram and carotid sphygmogram.



A.

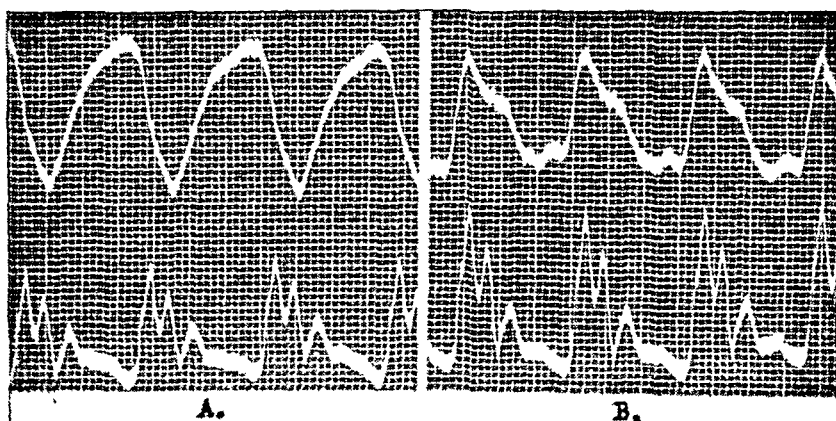


B.

FIG. 15. Bundle-branch block.

Subjects with arteriosclerotic heart disease and classical electrocardiographic evidence of bundle-branch block.

A—Right bundle-branch block. Ejection on pulmonary artery EKY (upper) 0.05 sec. behind that on carotid (middle), i.e.  $P_{Ac} = -0.05$  sec. Lower curve ECG—Lead II. B—Left bundle-branch block. Ejection on pulmonary artery (upper) 0.07 sec. ahead of carotid (lower), i.e.  $P_{Ac} \approx 0.07$  sec. These are significant variations from normal  $P_{Ac} + 0.03$  to  $-0.01$  sec.<sup>17</sup>



A.

B.

FIG. 16. Aortic regurgitation—subject with luetic aortitis and enlarged left ventricle. A—Middle left ventricle (RAO). Ascending and descending limbs from V-shaped trough with absence of complexes associated with isometric contraction and isometric relaxation on all views. Carotid sphygmogram shows systolic collapse. B—Ascending aorta, note absence of incisura.



in what specific types of cardiovascular disease pathognomonic EKY patterns appear and just what clinical value the instrument will have.\*

### CONCLUSIONS

1. The principles of the electrokymograph, the technic of its application and method of interpreting the records have been presented.

2. Electrograms from normal subjects and from selected subjects with cardiovascular disease have been demonstrated.

3. The instrument provides a valuable aid for studying the physiology of the cardiovascular system in human subjects and it warrants continuing evaluation of its possible clinical application.

### BIBLIOGRAPHY

1. CHAMBERLAIN, W. E., and DOCK, W.: The study of the heart action with the roentgen cinematography, *Radium*, 1926, vii, 185.
2. HIRSCH, I. S.: The recording of cardiac movements and sounds by the roentgen ray (kymophonoroentgenography), *Radium*, 1934, xxii, 403.
3. HIRSCH, I. S.: The application of kymoroentgenography to the diagnosis of cardiac disease, *Radium*, 1934, xxii, 720.
4. STUMPF, PL., WEBER, H. H., and WELTZ, G. A.: *Roentgenkymographische Bewegungslehre innerer Organe*, Leipzig, Thieme, 1936.
5. HECKMAN, K.: Moderne Methoden zur Untersuchung der Herz pulsation mittels Roentgenstrahlen, *Ergebn. inn. Med.*, 1937, lii, 569.
6. MARCHAL, M.: The registration of pulsations of the lung parenchyma and the cardiovascular system by kine-densigraphy, *Arch. d. mal. du coeur*, 1946, xxxix, 345.
7. HJELMAR, GUNNAR: The registration of the movements of the heart with Geiger-Mueller counter and synchronous electrocardiography, *Acta Radiologica*, 1946, xxvii, 334.
8. HENNY, G. C., and BOONE, B. R.: Electrograms for recording heart motion utilizing the roentgenoscope, *Am. Jr. Roentgenol. and Rad. Therapy*, 1945, liv, 217.
9. HENNY, G. C., and BOONE, B. R.: Electrograms for recording heart motion, improved type, *Am. Jr. Roentgenol.*, 1947, lvii, 409.
10. GILICK, F. G., BOONE, B. R., HENNY, G. C., and OPPENHEIMER, M. J.: The electrokymograph: application as a photo-electric plethysmograph, *Fed. Proc.*, 1946, Part II, 33.
11. HENNY, G. C., BOONE, B. R., and CHAMBERLAIN, W. E.: The electrokymograph: an apparatus for recording motion (for example, that of the heart border shadow), *Fed. Proc.*, 1946, Part II, 44.
12. BOONE, B. R., GILICK, F. G., CHAMBERLAIN, W. E., and OPPENHEIMER, M. J.: Electrograms of heart border motions: principles of record interpretation, *Fed. Proc.*, 1946, Part II, 9.
13. CHAMBERLAIN, W. E., BOONE, B. R., ELLINGER, G. F., HENNY, G. C., and OPPENHEIMER, M. J.: Asynchronism of ejection of the ventricles as measured with the electrokymograph, *Fed. Proc.*, 1947, vi, 88.
14. BOONE, B. R.: Application of the electrokymograph to the study of cardiovascular physiology, *Abstracts of Communications, XVII International Physiological Congress*, 5.

\* Since this paper was submitted, additional papers on the clinical application of electrokymography have been published or have been accepted for publication. References to this material have been added.<sup>30, 31, 32, 33, 34</sup>

## SECONDARY AMYLOIDOSIS IN SPINAL CORD INJURY \*

By CHARLES EDWARD THOMPSON, M.D., F.A.C.P., *Chicago, Illinois*, and  
MARION LEE RICE, JR., M.D., *Memphis, Tennessee*

RECENT reviews of the literature reveal an awakening of interest in the study of amyloidosis.<sup>1, 2, 3, 4, 5</sup> The occurrence of this lardaceous pathological process in relationship to spinal cord injury had not been noted previously, with the exception of a case reported in 1867 by Fagge.<sup>6</sup> A large number of spinal cord injuries, resulting from World War II, are under observation in Veterans Administration hospitals. Sufficient time has now elapsed for these patients to be subjected to the effects of wasting disease, tissue atrophy and repeated infections. Secondary amyloidosis in this group of patients then might be expected to occur.

The purpose of this manuscript is to report four cases of secondary amyloidosis found at autopsy in patients with spinal cord injury and to discuss the clinical significance of this process.

*Case 1.* This 22 year old white male was injured in a fall November 13, 1942. Following this injury a physiologically complete myelopathy at the level of D-4 was present. His course subsequent to this event was the usual one of decubitus ulcer and recurrent urinary infection with renal vesicular calculi. The patient maintained a poor state of nutrition throughout this time.

On March 28, 1947, he was admitted to this hospital for treatment and care of his spinal cord injury. At this time he was markedly undernourished and had multiple decubitus ulcers. His urinary status was as follows: suprapubic catheter, penoscrotal fistula, bilateral renal calculi and chronic cystitis. The following were the laboratory data: urine albumin 2 plus, no casts or cells in urine; red blood cells 3,400,000; hemoglobin 12 gm.; total protein 6.5 with A/G ratio 1.5. X-ray pyelography revealed nonfunction of left kidney and small multiple calculi in right kidney.

Course in Hospital: A high protein, caloric and vitamin diet was instituted with improvement of ulcers but only slight nutritional response. Gross hematuria developed in July. Slight rectal bleeding occurred in September. Proctoscopic examination on September 10, 1948, revealed edema and injection of the mucosa. The patient suddenly became nauseated and oliguria appeared. Blood pressure at this time was 50 mm. of mercury systolic and 30 mm. diastolic. Red blood cells 3,300,000, hemoglobin 9.2 gm., and non-protein nitrogen 56 mg. per cent. Cystoscopic examination revealed calculi had moved into the right ureter. An emergency right nephrotomy was performed to establish urine flow. There was no improvement in renal function from this procedure. Shock continued. On September 13, 1947, jaundice developed. The icteric index was 33, with no urobilin in feces or urine. On September 16, the non-protein nitrogen was 123 mg. per cent; the urine contained 4 plus albumin; the

\* Received for publication March 9, 1948.

From Paraplegia Service, Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis, Tennessee. Published with permission of Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

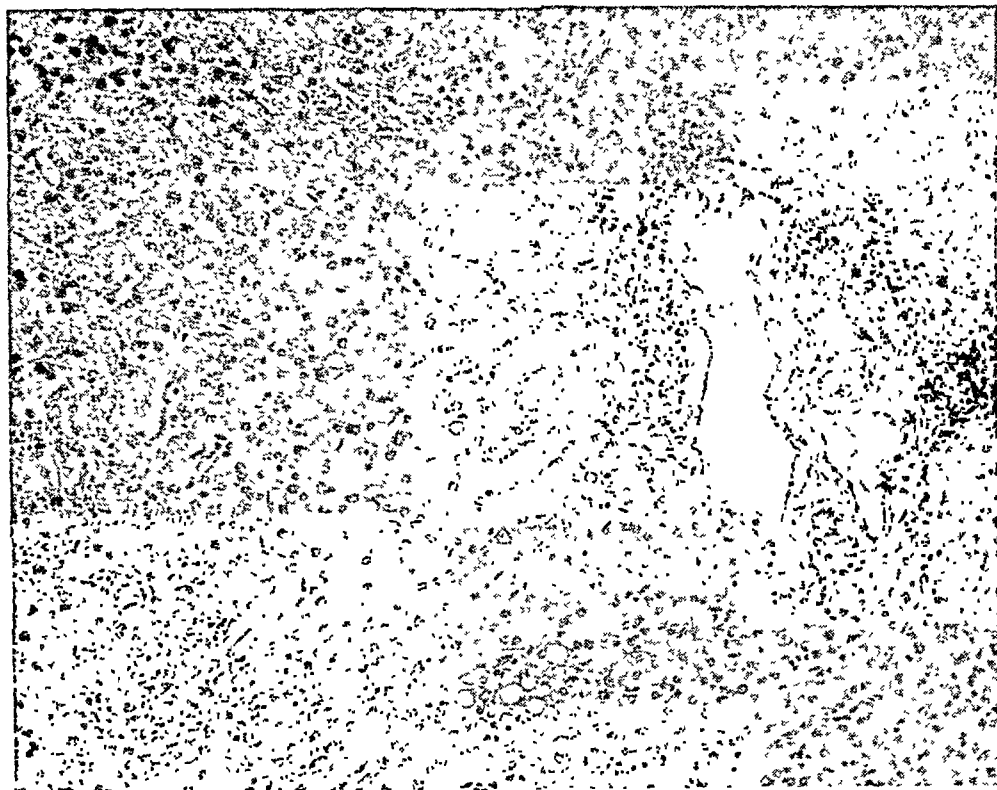


FIG. 2. *Case 1.* Liver. Showing fibrosis and round cell infiltration with pale staining amyloid material replacing the parenchymal cells.

**Pathological Findings:** Amyloid deposits in the spleen and kidneys were found at autopsy (figures 5 and 6). There was a bronchopneumonia and pulmonary infarct (left). A gastric and duodenal ulcer were also noted.

*Case 3.* In April, 1945, a 25 year old male received a gunshot wound, fracturing the fourth thoracic vertebra. A complete transverse myelopathy followed this injury. Laminectomy and suprapubic cystotomy were performed three weeks after injury. Decubitus ulcers of the ischium and trochanteric areas developed early. The ischial decubitus ulcers were closed surgically, but the ulcers in the trochanteric region at no time healed. Before admission to this hospital there was no history of renal infection or of renal calculi.

He was admitted to this hospital on January 16, 1948, as a transfer from another hospital. There were large decubitus ulcers over both trochanters, the right thigh and the sacrum. One month before admission, he suffered third degree burns of both feet. These extremities became infected following the burn, and bilateral edema was present on admission. During December, 1947, while still out of the hospital, the patient developed several loose stools which were controlled with paregoric and bismuth. Several days before his admission to this hospital he developed severe diarrhea, that was uncontrolled by previous measures. Laboratory data were negative, except for a mild hypochromic anemia and low serum protein (5 grams with A/G ratio of 1 to 1). X-ray study of kidneys, ureter, and bladder revealed no calculi.

**Course in Hospital:** Patient was placed on a low residue diet and given sulfaguanidine and paregoric to relieve diarrhea. Bacteriological examination of stools was negative throughout the illness. On January 19, 1948, three days after admission a 3 plus albumin was present in the urine. This albuminuria continued, varying between one and three plus. The severity of the diarrhea fluctuated, but was never



FIG. 4. *Case 1.* Adrenal cortical tissue almost completely infiltrated with amorphous, pink staining amyloid material.

on June 6, 1946, a decubitus ulcer of the right hip, a stag-horn calculus in the right kidney, and osteomyelitis of L-1 and L-2 vertebrae was present. In September 1946, the patient developed infectious hepatitis. Calculi developed in the right kidney and were removed November 8, 1946. A transurethral vesical resection was performed in March, 1947, with improvement of renal function. Several episodes of urinary infection occurred and calculi developed in both kidneys. Patient left the hospital against medical advice for six months. On September 6, 1947, he was admitted with the previous diagnoses, plus a draining sinus in the suprapubic ulcer and multiple rat bites of the lower extremities. His course following readmission steadily declined. The bilateral stag-horn calculi increased in size but the patient's general condition was too poor to consider further surgical intervention. There were repeated episodes of urinary infection and one plus to three plus albumin was always present. Liver function testing on January 15 showed bromsulfalein 20 per cent, cephalin flocculation 3 plus in 48 hours, total protein 6.5 grams and A/G ratio 1.2 to 1.

In January, 1948, amyloidosis was suspected but Congo red test was negative. Examination of the gingival tissue showed no evidence of amyloidosis. On February 3, 1948, suprapubic cystotomy was performed to increase renal function. On February 27, 1948, a spontaneous femoral thrombophlebitis, left, occurred and a bilateral femoral vein ligation was performed. The patient lost strength rapidly. Transient edema of face, genitalia and abdomen was observed the latter part of March. Total proteins at that time were 4.7 grams with .6 to 1 A/G ratio. Severe, uncontrollable diarrhea developed about one month later. Non-protein nitrogen gradually rose to 74 mg. per cent on April 4, 1948. One week before death the urine became grossly bloody. Oliguria developed and was accompanied by clinical evidence of azotemia.

On May 12, 1948, respirations became labored and shallow. Constant projectile vomiting and Cheyne-Stokes respiration developed, followed by death.

**Pathological Findings:** At autopsy, amyloid deposits were noted in the kidneys and adrenal cortex. There was also periportal hepatic cirrhosis and ulcerative colitis.

### DISCUSSION

Spinal cord injury is accompanied by a triad of inflammatory processes: decubitus ulcers, chronic osteomyelitis and urinary infections. In addition to this triad there is a profound disturbance of metabolism that has not been elucidated. The fact that these patients now live long enough to be encumbered by the above processes makes amyloid degeneration a distinct possibility.

The clinical findings of secondary amyloidosis vary with the organ involved and the amount of amyloid deposited. The primary disease often masks the findings.<sup>7, 8, 9</sup> If the liver and spleen are involved, these organs usually will be palpable. Abdominal distention may accompany these findings. Purpura has been reported in several cases with splenic amyloidosis.<sup>10</sup> Jaundice, seen in Case 1, is extremely rare, having occurred only four times in the previous literature.<sup>11, 12</sup> Albuminuria obviously is a consistent sign when amyloid degeneration involves renal tissue. If albuminuria is excessive, hypoproteinemia will result. The edema of hypoproteinemia appears late in the course of the disease. Hyaline and granular casts may also appear. There is loss of the power of concentration of the kidney due to tubular damage. The severe azotemia that preceded coma and death in the cases presented is an unusual finding in amyloid disease.<sup>7</sup> When renal insufficiency and uremia occur, the process is irreversible and death is rapid as is illustrated by these cases. Adrenal involvement is a common finding.<sup>10</sup> Addison's disease as a result of amyloid deposits in the adrenal is rare; however, three of these cases presented the clinical picture of subacute adrenal cortical insufficiency.

The clinical diagnosis of amyloidosis in spinal cord injury is difficult because the findings described above are present in the ordinary complications of this injury. Malnutrition and metabolic disorders occur soon after spinal shock. Hepatomegaly is seen frequently. It has been noted in 33 of 250 patients on the Paraplegia Service here. The cause of this enlargement of the liver has not been elucidated. Cases 1 and 3 are the only patients of the 33 mentioned above in which this hepatomegaly proved to be associated with deposits of amyloid in the liver. Albuminuria is also a frequent finding resulting from urinary infection and calculi in the bladder and kidney accompanying spinal cord injury.

It is interesting to attempt to explain the cause of the non-specific bloody diarrhea in the cases presented. Two peptic ulcers were present at necropsy (Cases 2 and 4), one gastric and the other duodenal. In Case 2 there was some evidence of bleeding from the gastric ulcer. Case 4 presented ulcerative colitis. There were no amyloid deposits in the gastrointestinal tract in

15. TARAN, A.: Improved Congo red test, *Jr. Lab. and Clin. Med.*, 1937, xxii, 975-977.
16. TARAN, A., and ESKSTEIN, A.: Standardization of the Congo red test, *Am. Jr. Med. Sci.*, 1942, cciii, 246-253.
17. BABER, M. D.: Amyloid macroglossia, *Lancet*, London, 1947, i, 210-211.
18. BANNICK, E. G.: Diffuse amyloidosis of unknown etiology, *Med. Clin. North Am.*, 1934, xviii, 411-422.
19. BANNICK, E. G., and BERKMAN, J. M.: Diffuse amyloidosis, clinical and pathological study, *Arch. Int. Med.*, 1938, li, 978-990.
20. CORBETT, R. W., and BRODERS, A. C.: Amyloidosis of the urinary bladder, *Jr. Urol.*, 1944, lii, 153-157.
21. DICK, G. F., and LEITER, L.: Development, localization and reabsorption of amyloid in rabbits, *Am. Jr. Path.*, 1941, xvii, 741-754.
22. DIXON, H. M.: Renal amyloidosis in relation to renal insufficiency, *Am. Jr. Med. Sci.*, 1934, clxxxvii, 401-411.
23. DUNN, T. B.: Relationship of amyloidosis and renal disease in mice, *Jr. Nat. Cancer Inst.*, 1944, v, 17-28.
24. HAYMAN, J. M.: Cecil's textbook of medicine, 1942, 5 ed., 1062-1063.
25. HYMAN, A.: Association of hypernephroma with amyloidosis of the kidney, *Jr. Urol.*, 1946, lvi, 303-309.
26. JAFFE, R. H.: Influence of diet in amyloidosis, *Arch. Path.*, 1926, i, 20.
27. JAFFE, R. H.: Amyloidosis produced by injection of protein, *Arch. Path. and Lab. Med.*, 1926, i, 25.
28. KU, D. Y., and SIMON, M. A.: Influence of various diets on mice, *Arch. Path.*, 1934, xviii, 245-251.
29. KRUMBHAAR, E. C.: Cecil's textbook of medicine, 1942, 5 ed., 1386.
30. KOLETSKU and STRECHER: Primary systemic amyloidosis, involvement of cardiac valves, joints and bones, with pathological fracture of femur, *Arch. Path.*, 1939, xxvii, 267-288.
31. LINDSAY, S., and KNORP, W.: Primary systemic amyloidosis, *Arch. Path.*, 1945, xxxix, 315-322.
32. MOSCHCOWITZ, E.: Clinical aspects of amyloidosis, *Ann. Int. Med.*, 1936, x, 73-88.
33. NOMLAND, R.: Localized (lichen) amyloidosis of the skin, *Arch. Dermat. and Syph.*, 1936, xxxiii, 85-98.
34. PEARSON, P., and RICE, MAURICE: Primary systemic amyloidosis; report of 2 cases in negroes with special reference to certain histological criteria for diagnosis, *Arch. Path.*, 1941, xxxii, 1-10.
35. PURCELL, H. M.: Localized amyloidosis of the urinary bladder, *U. S. Naval Med. Bull.*, 1946, xlv, 1607-1610.
36. REIMANN, H. A., and EKLUND, C. M.: Primary amyloidosis limited to tissues of mesodermal origin, *Am. Jr. Path.*, 1935, xi, 977-988.
37. ROSENBLATT, M. B.: Amyloid nephrosis, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 558-567.
38. SELIKOFF, I. J.: Gingival biopsy for diagnosis of generalized amyloidosis, *Quart. Bull. Sea View Hosp.*, N. Y., 1946, viii, 4.
39. SOLOMON, W.: Amyloidosis in chronic atrophic arthritis, *Ann. Int. Med.*, 1943, xviii, 846-850.

TABLE I  
Showing Clinical Data on Patients Discharged from General Hospital with Pneumonia Preceding Tuberculosis  
(Only those included, on whom adequate information available)

Name	Sex	Age	X-Ray Reading Gen. Hospital	WBC— Gen. Hosp.	Temperature	Elapsed Interval	X-Ray TBC Hosp.
1. H. W.	WF	39	Mottled fibrous densities in left first interspace. Densities in lower left chest and hilum. No essential changes, later. Considered atypical pneumonia.	8,400	104°(R) on admission. On penicillin and sulfadiazine, drop to normal in five days but persistent low grade fever to 99.6° on discharge.	11 mos.	Diffuse infiltration involving entire left lung, also infiltration at right base. Positive sputum.
2. E. B.	CM	47	Mottled shadows, density over entire left lung and lower portion of right. Marked clearing hilar region later.	18,800–12,000 11,000–14,000	104 to 105° on admission—gradually subsiding but never disappearing completely. No chemotherapy.	5 mos.	Right lung clear. On left—infiltration from apex to fourth rib with mottling to base.
3. J. H.	CM	47	Large area of consolidation base of right lung with fibroid infiltration left apex. Discharged, diagnosis—acute lobar pneumonia RLL type undetermined with delayed resolution.	32,400	Temperature fell by crisis. No chemotherapy.	Approx. 3 yrs.	1st admission for TBC, x-ray reading not available.
4. J. M.	CM	48	Consolidation right upper lobe.	2,500–17,400	104 to 101° to low grade fever after one week. Sulfonamides.	3 mos.	Infiltration right upper lobe.
5. J. F.	WM	71	Pneumonic density, left upper lobe.	8,200–9,000	100–104° for nine days, went down to 99.4°.	2 mos.	Bilateral apical disease minimal.
6. E. R.	WM	50	Consolidation upper $\frac{2}{3}$ right lung, no change until two months later when slight clearing was reported.	5–8,000	From 105° to normal in five days. Low grade thereafter.	1 year	Far advanced disease right upper lobe with cavity.

The patient had pneumonia without tuberculosis. The illness may or may not have contributed to the later development of tuberculosis. (2) There was a pneumonia superimposed on a tuberculous infection. (3) The findings were misinterpreted as being due to pneumonia when actually due to tuberculosis. It is probable that the largest number of cases fall in the last group, of which the following case histories are illustrative:

A 38 year old white man was admitted with tuberculosis on June 27, 1945. He had complained of malaise and fatigability for two years but of no other significant symptoms. In the late winter of 1944, he developed a cold with a fever and cough.



FIG. 1a. Consolidation right upper lobe. Diagnosis: pneumonia.

This was diagnosed as bronchopneumonia and after treatment with sulfonamide and bed rest at home, he felt fairly well. In March 1945, there was another acute episode and again the symptoms subsided on rest and chemotherapy. In May 1945, the symptoms recurred. A roentgenogram showed far advanced tuberculosis.

A 50 year old white man was first admitted to Baltimore City Hospital on March 18, 1942. His temperature was 105° F. and a roentgenogram showed consolidation of the upper two-thirds of the right lung. His temperature subsided within five days



temperature was  $100^{\circ}$  rectally with a leukocyte count of 20,400. Physical and roentgenologic signs indicated lobar infiltration at the right base. In spite of physical signs at the right apex there was no roentgenologic evidence of disease in that area. No pneumococci were found in the sputum but on two occasions acid fast organisms were found. He was transferred to the City Hospitals, where the positive sputum was confirmed. The consolidation at the right base cleared; a minimal degree of infiltration at the right apex remained. He signed out after a few months of hospital care. In 1946, he was re-admitted in a critical condition with far advanced disease.



FIG. 2a. Acute onset of illness, consolidation of left upper lobe. Five weeks later: some resolution of process. Sputum negative for acid fast organisms.

A white man of 55 was first admitted to the City Hospitals in March of 1944. The temperature was  $103^{\circ}$ , the leukocyte count 16,500 with 89 per cent polymorphonuclears. The roentgenogram showed consolidation of the left upper lobe. The temperature returned to normal slowly while the patient was under treatment with sulfadiazine. Five sputum examinations were negative for acid fast organisms. No pneumococci were detected. In October 1946, he was admitted again with an almost identical story. The temperature was  $105^{\circ}$  and the white count 23,000. He was severely dyspneic. The temperature and white count returned to normal after 24 hours as did his respiration, during the administration of penicillin. The sputa were

(b) The white count may be elevated in tuberculosis to as high levels as in lobar pneumonia.<sup>2</sup> It has been stated that one-fourth of the patients with far-advanced disease have white counts between 12,000 and 18,000, on admission.

(c) The fact that the tuberculous process may be restricted to a lower lobe may suggest a non-tuberculous pneumonia.<sup>3</sup>

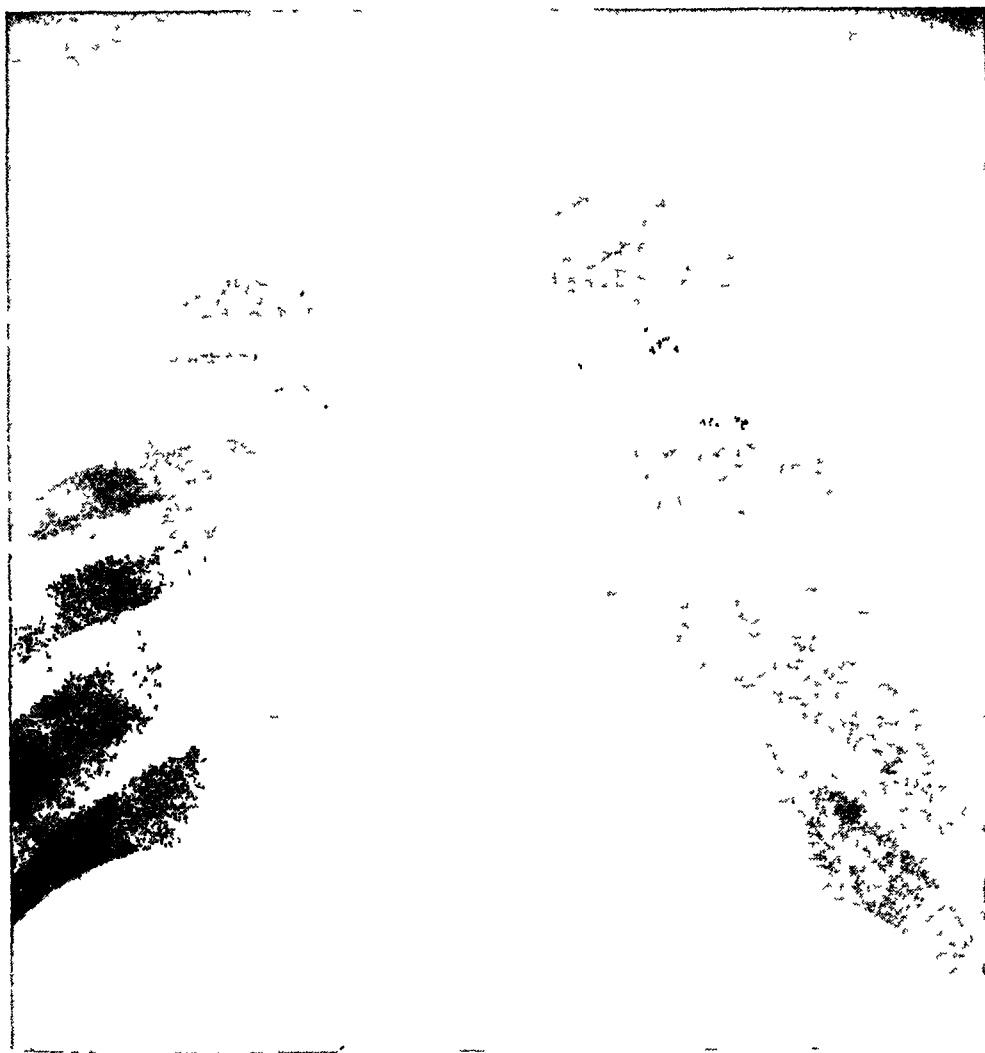


FIG. 3a. Film taken on outpatient basis. No acute symptoms, no sputum obtained. Diagnosis of tuberculosis made because of film.

(d) In early tuberculosis prior to caseation there may be great difficulty in obtaining a positive sputum.

(e) Even the course of the disease, which is usually decisive, may at times prove misleading. While in general non-tuberculous pneumonias resolve in a few weeks and tuberculous infiltrations persist, there are exceptions to both of these rules. Primary atypical pneumonia has been known to give roentgenographic changes for three months.<sup>6</sup> On the other hand, exudative, tuberculous lesions may disappear within the same length of time.

discussing the process of resolution states that it proceeds slowly and stops at the barriers of unresolvable, caseous centers. It is certainly conceivable that, if there is minimal caseation, resolution may be complete enough so that the residual caseous center may be invisible on the roentgenogram.

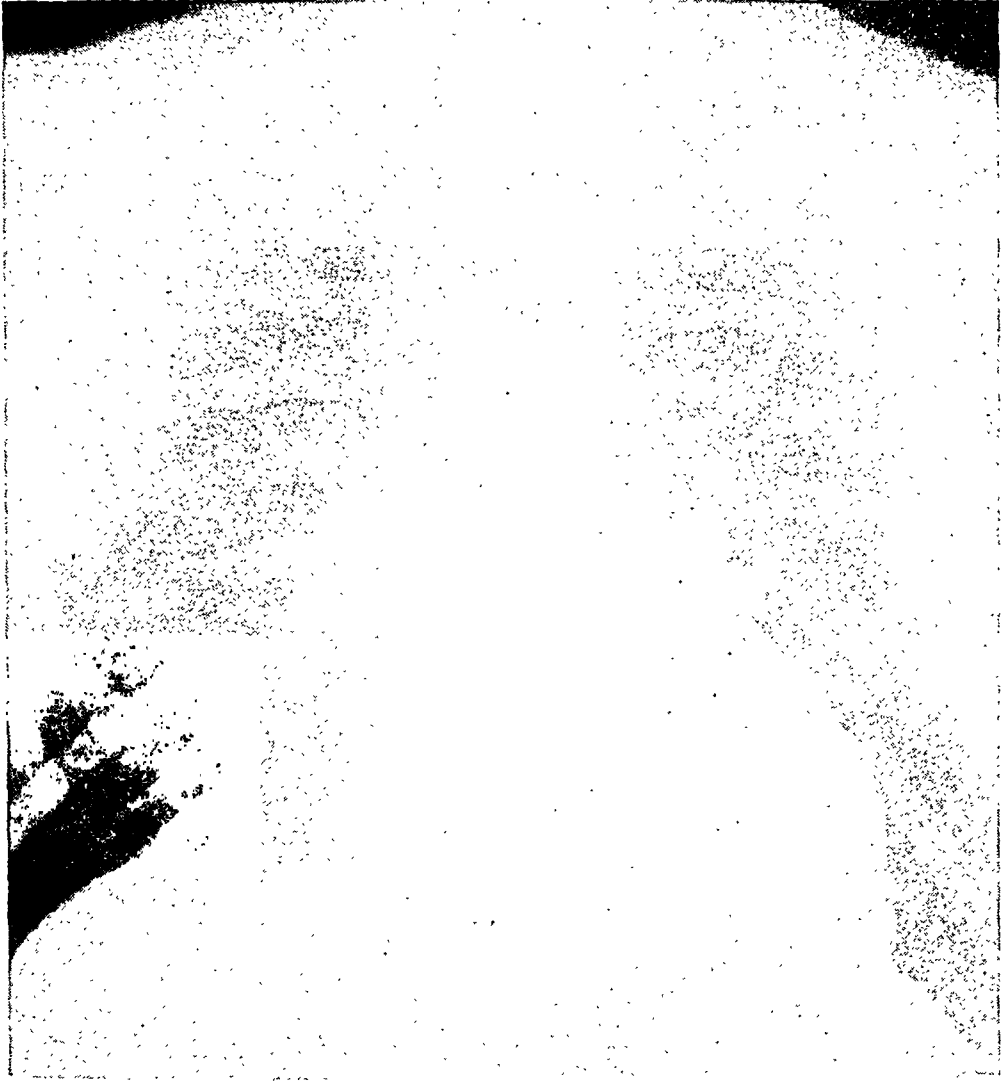


FIG. 3c. Readmission to tuberculosis division 15 months later. Positive sputum.

In view of these facts, it is not difficult to understand why difficulties in diagnosis may arise as between a non-tuberculous pneumonia and pulmonary tuberculosis.

#### DISCUSSION

Very little is found in our literature concerning an antecedent history of pneumonia in tuberculosis. Flick<sup>7</sup> is quoted as stating that one-fifth of all tuberculous patients gave previous histories of pneumonia. Baum and Amberson<sup>8</sup> consider the possibility that these and other reported instances

pital, it is evident that the possibility of this costly mistake in diagnosis is increased when the patient is treated at home. In recent years with the advent of chemotherapy, and antibiotics, home treatment of acute respiratory disease is more common. There is a tendency to class resistant cases as primary atypical pneumonia. It cannot be too strongly emphasized that the possibility of tuberculosis as the etiologic factor should be kept in mind in all acute pulmonary disease. Sputum examinations and follow-up chest films are of great importance if error is to be avoided.

### SUMMARY

Of 500 unselected cases of tuberculosis, 14.2 per cent gave a history of acute illness diagnosed as pneumonia within the period in which tuberculosis might have been expected to be present. This incidence is far greater than would be expected from the reported coincidence of pneumonia and tuberculosis. The findings in an acute tuberculosis may simulate those of pneumonia. There is evidence that in certain of these tuberculous patients, the symptoms resulting in a diagnosis of pneumonia were, in fact, due to tuberculosis.

### BIBLIOGRAPHY

1. KINGHORN, H. M.: The diagnosis of tuberculosis, *Jr. Am. Med. Assoc.*, 1940, cxv, 1614-1620.
2. STOBIE, W., ENGLAND, N. A., and McMENEMY, W. H.: Interpretation of the hemogram in tuberculosis, *Am. Rev. Tuberc.*, 1942, xlv, 1-26.
3. SOKOLOFF, M. J.: Lower lobe tuberculosis, *Radiology*, 1940, xxxiv, 589-594.
4. AMBERSON, J. B., JR.: The process of resolution in pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1936, xxxiii, 269-301.
5. ORNSTEIN, G. G., ULMAR, D., and DITTLER, E. L.: Benign acute pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1931, xxiii, 223-247.
6. GOODRICH, B. E., and BRADFORD, H. A.: Recognition of virus type pneumonia, *Am. Jr. Med. Sci.*, 1942, cciv, 163-179.
7. FLICK, K. F.: Third Annual Report (1905-1906), Henry Phipps Institute, Philadelphia (quoted by Baum and Amberson).
8. BAUM, O. S., and AMBERSON, J. B., JR.: Non-tuberculous pulmonary infections complicating pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1943, xlv, 243-279.
9. PINNER, M.: Pulmonary tuberculosis in the adult, 1945, Charles C. Thomas, Springfield, p. 270.
10. FARBER, J. E., and CLARKE, W. T.: Unrecognized tuberculosis in a general hospital, *Am. Rev. Tuberc.*, 1943, xlvii, 129-134.
11. RIST, E.: The sudden onset of lung tuberculosis and its lobar localization, *Canadian Med. Assoc. Jr.*, 1929, xxi, 143-152.
12. PEDIGO, G. W., JR., and COLEMAN, E. O.: Pneumococcal pneumonia complicating pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1941, xliii, 258-262.
13. HOGAN, G. F.: Non-tuberculous pneumonia complicating pulmonary tuberculosis, *New England Jr. Med.*, 1945, ccxxxiii, 547-556.

before a diagnosis of atypical lichen planus could be made. During 1944 and early in 1945, many who were interested in the clinical study of these diseases felt that enough clinical evidence existed to ascribe a common etiological denominator to all three of these conditions.

### CLINICAL MANIFESTATIONS

*Age:* In one of our series of 21 unselected cases of atypical lichen planus in enlisted men who were being observed at one time in a ward of an Army General Hospital in New Guinea, the range of ages was from 24 to 46. The average age for the group was 31. This was older than the average age of the enlisted personnel suffering from other diseases in the hospital. The early impression that the disease was more common and more severe in the older age group seemed to be consistently borne out as greater experience with this disease was had.

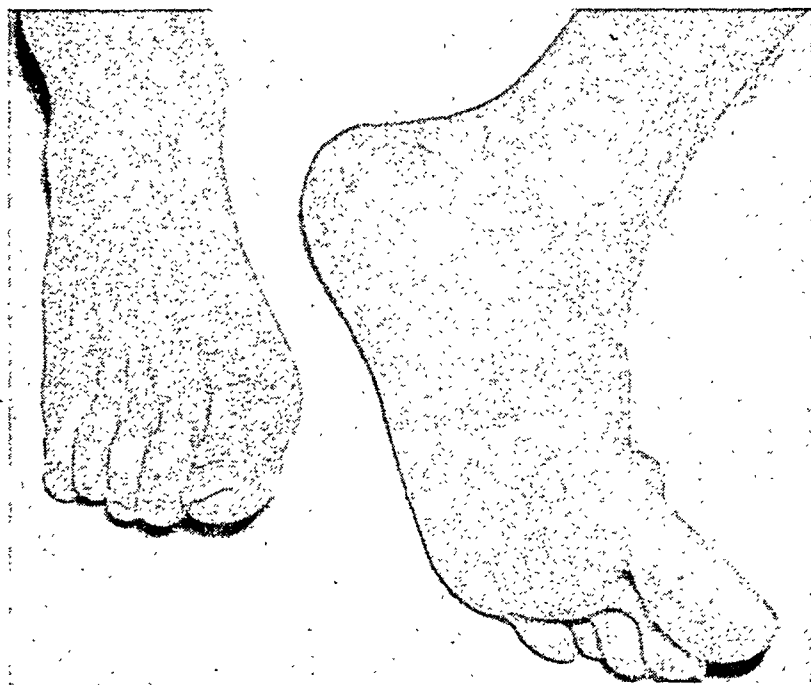


FIG. 1. Case A. B., showing extremely hypertrophic lesions.

*Time of Onset:* In the same group of 21 patients, a striking similarity in the time of occurrence of the disease was apparent. No patient in our series developed his disease prior to his being in New Guinea or, as later became evident, in the Philippine Islands, for two months. With one exception, each of the 21 patients observed his initial lesion two to five months after his arrival in New Guinea. One of the 21 did not develop his eruption until nine months had elapsed. This inclination for the disease to occur during this interval of time became an important diagnostic factor as it became apparent that the disease manifested itself neither within the first

to that seen the year before in New Guinea and in so far as we were able to ascertain, this disease had never been described as an affliction of Americans or Filipinos living in the Philippine Islands before the war.

*Sex:* The disease occurred among male and female personnel with equal severity. The relative incidence in each could not be determined.

*Race:* Atypical lichen planus was more common in soldiers of the Caucasian race. Few cases appeared among Negro troops, but they had some. One of our very sick patients was an American soldier of Japanese descent.



FIG. 2. Case C. D., discrete and confluent hypertrophic lesions in a Chinese-American soldier.

Another one of our patients was an American of Chinese origin. One very sick patient, an elderly Filipino Scout, developed his disease not during Japanese occupation but rather afterwards when he was recalled to service.

*Description of Lesion:* The characteristic lesion of atypical lichen planus is a well defined, flat-topped, hypertrophic papule, the border of which is irregular and angular. It has a violaceous hue of varying intensity so that some lesions are almost a deep slate blue color. The surface has fine scales and is striated. At first the lesions are discrete but later they tend to

man<sup>6</sup> reported a study on the blood findings in the anemia associated with this disease. They reported granulocytopenia, thrombocytopenia, and normocytic anemia. They likened their findings to those of severe toxic aplasia such as that resulting from benzol.

### PATHOLOGY

Rosenthal<sup>2</sup> reported an extensive study of the pathology of the disease. He describes the pathological changes as occurring in three separate phases, the acute, subacute, and chronic. In the acute phase, the characteristic

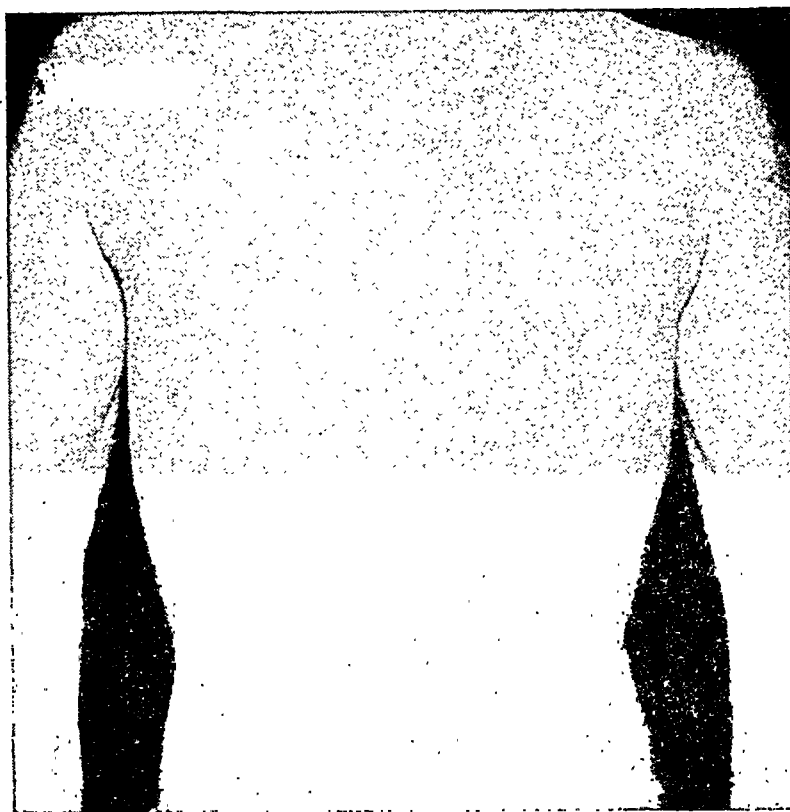


FIG. 3. Case C. C., widespread distribution of atypical lichen planus, demonstrating lichenification, follicular hyperkeratosis, "lace-work" scaling.

changes appeared to be thickening of the stratum corneum, widened hair follicles filled with keratin, acanthosis and marked cellular infiltration with polymorphonuclears, particularly eosinophiles. In the subacute phase there was further widening of the keratin layer. There was less inflammatory infiltration and some histiocytic infiltration. There was also degeneration of the stratum basalis. In the chronic phase the inflammatory reaction was less marked with only scattered inflammatory cells. The featured findings were an acanthosis, plugging of the hair follicles, and increased pigmentation in the basilar layer. This pigment stained with Becker's stain, a non-specific stain for melanin. Two cases of aplastic anemia were observed by Rosenthal,

Of the several hundred cases treated and observed by us in the hospital for an average of six weeks only four showed signs of definite improvement over any significant period of time. All four had had their atabrine withdrawn prior to our being able to make this observation. Many others who likewise had had their atabrine withdrawn showed no improvement while they continued under our observation overseas.



FIG. 4. Case C. W., dystrophy of nails with loss of left index finger-nail. Note, too, the scalp lesions with alopecia areata.

No specific information on the mortality of this clinical triad is available in the literature reviewed. From what has been observed it appears that the mortality was very low and due to complications mentioned before, namely agranulocytosis, aplastic anemia and cerebral hemorrhage.

#### ETIOLOGY

It is reported<sup>1</sup> that Nisbet and Schmitt first suggested that atabrine might be the cause of this disease. Extensive skin patch-testing by us and



isolated observation. No other evidences of specific nutritional deficiency states appeared with significant regularity in our patients.

It was suggested that the subjective improvement or the slowing of the disease that often followed hospitalization might have been due to removal from the excessive exposure to tropical sun. As a basis for this, it has also been suggested that atabrine, a fluorescent acridine dye, might, in some individuals, produce a cutaneous photosensitivity. There is no actual proof to support this interesting hypothesis. One of our patients accepted the rôle of having one hand covered with a gauze bandage in which there had been



FIG. 5. Case F. E., generalized edema is present. This case of atypical lichen planus is associated with symmetrical exudative eczematoid features. Discoloration of skin and nails due to potassium permanganate.

incorporated some black paper. After six weeks, both the bandaged and unbandaged hand appeared to have progressed equally.

#### TREATMENT

All patients in whom a diagnosis of atypical lichen planus was made were evacuated to the United States regardless of the extent of the disease. This policy held as well for those patients who had an exfoliative dermatitis. Patients with the eczematoid dermatitis were sent back to duty if, under treatment, the eczematoid dermatitis disappeared and there were no evi-

## SUMMARY AND CONCLUSIONS

1. The history of the disease, atypical lichen planus, was described, and its likely etiological relationship to a peculiar eczematoid dermatitis and a frequently occurring exfoliative dermatitis was discussed.

2. The clinical manifestations, pathology, and laboratory findings were described.

3. Prolonged ingestion of atabrine is considered to be the presumptive basic cause of the disease. Other factors, however, may be secondarily operative in its production.

4. It is the opinion of the author that atypical lichen planus is merely a cutaneous manifestation of a generalized systemic disorder.

5. Few instances of improvement were observed while the patients remained overseas. Because of this, plus the fact that the disease is both disabling and progressive, all patients with atypical lichen planus were evacuated to the United States.

6. Withdrawal of atabrine, and the maintenance of adequate nutrition were applied in all cases. Local therapy was found to be of only temporary value when exudation was present.

7. The value of infusions of plasma and whole blood in the management of the exudation and edema was stressed.

8. Penicillin is a valuable aid in treating those cases exhibiting secondary infection.

Photographs by 4th Med. Museum and Arts Dept., A. U. S.

## BIBLIOGRAPHY

1. Special Article, Evaluation of untoward reactions attributable to atabrine, Bulletin U. S. Army Med. Dept., 1945, iv, 653-659.
2. ROSENTHAL, JULIUS: Atypical lichen planus, Am. Jr. Path., 1946, xxii, 473-491.
3. GOLDBERG, L. C.: An unusual lichenoid dermatosis, Jr. Am. Med. Assoc., 1946, cxxx, 775-781.
4. DANTZIG, LOUIS, and MARSHALL, L. E.: Tropical lichen planus—New Guinea variety, New York State Jr. Med., 1946, xlvi, 991-995.
5. EPSTEIN, IRVIN: The lichen planus eczematoid dermatitis complex of the Southwest Pacific, Bull. U. S. Army Med. Dept., 1945, iv, 687-695.
6. MOST, HARRY, and HAYMAN, J. M.: Recovery from severe hypoplastic anemia associated with atypical lichen planus, Bulletin U. S. Army Medical Dept., 1946, v, 339-342.
7. VORHAUS, M. G., GOMPERTZ, M. L., and FEDER, AARON: Clinical experiments with riboflavin, inositol, and calcium pantothenate, Am. Jr. Digest. Dis., 1943, x, 45-48.
8. FEDER, AARON: Therapy unit for patients with skin diseases, Bulletin U. S. Army Medical Dept., 1946, v, 343-345.

history except that since discharge from the Army several years previously he had been imbibing alcoholic beverages heavily. This is mentioned because it is the impression of some that idiopathic venous thrombosis and pulmonary embolism are more common in chronic alcoholics.<sup>12</sup> Review by systems was completely negative except for the information that the patient had had frequent colds during the past winter, the last one six weeks prior to admission.

On December 9, 1947, the patient went to bed at 9 p.m. feeling as usual except that his feet felt unusually cold, for which reason he wore a pair of socks to bed. For three weeks previous, the patient had noticed some stiffness and soreness in his calf muscles upon arising in the morning, which would disappear when he became active. He attributed these symptoms to playing football with his young children during the preceding month. He had noticed no stiffness or soreness in the thighs. The patient arose at 6:30 a.m. December 10 and went downstairs to his desk to work on some company reports. He had been working about 10 minutes when he suddenly became weak and broke into profuse perspiration. He went to the kitchen, wiped off his face, then returned to his desk. A few minutes later he had a chilly

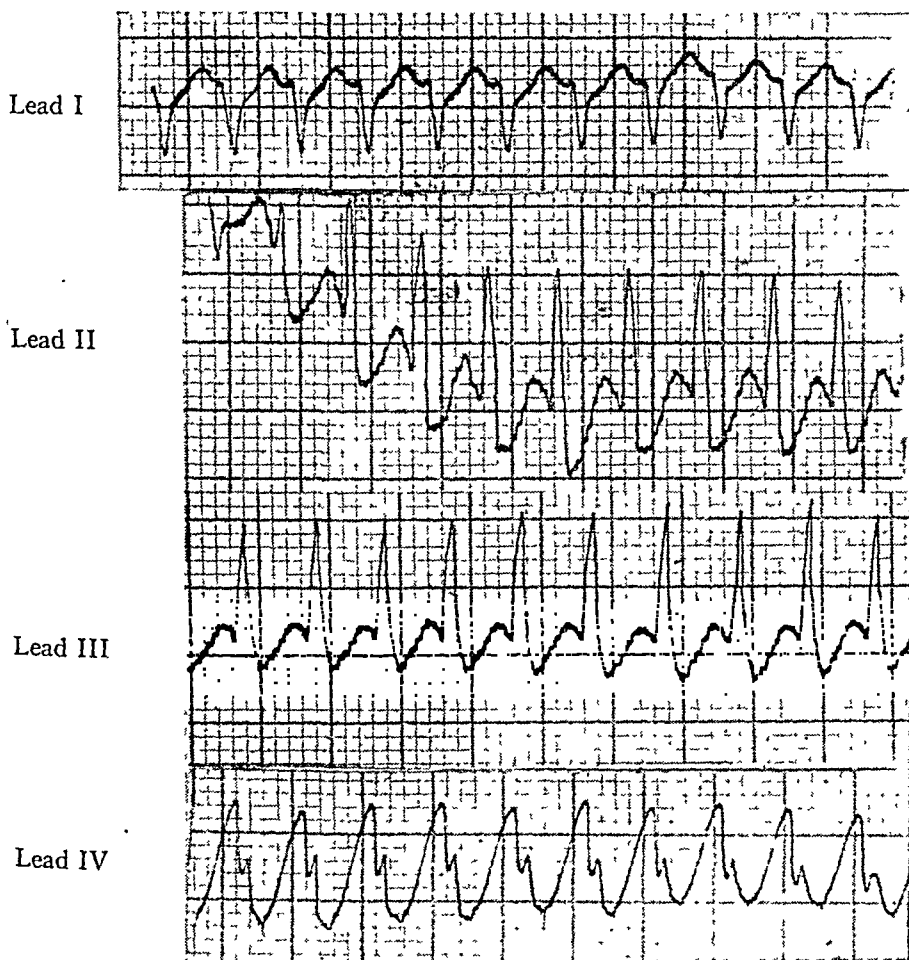


FIG. 1. Electrocardiogram taken two hours after fainting attack and one hour after onset of tachycardia. Rate is 300 to 315 per minute. Note the extreme right axis shift. Because of the extremely rapid rate and the absence of a period of electrical quiescence in the auricles in all leads, the rhythm is interpreted as auricular flutter with 1:1 conduction, although supraventricular tachycardia can not be definitely ruled out. (Compare with figure 2.)

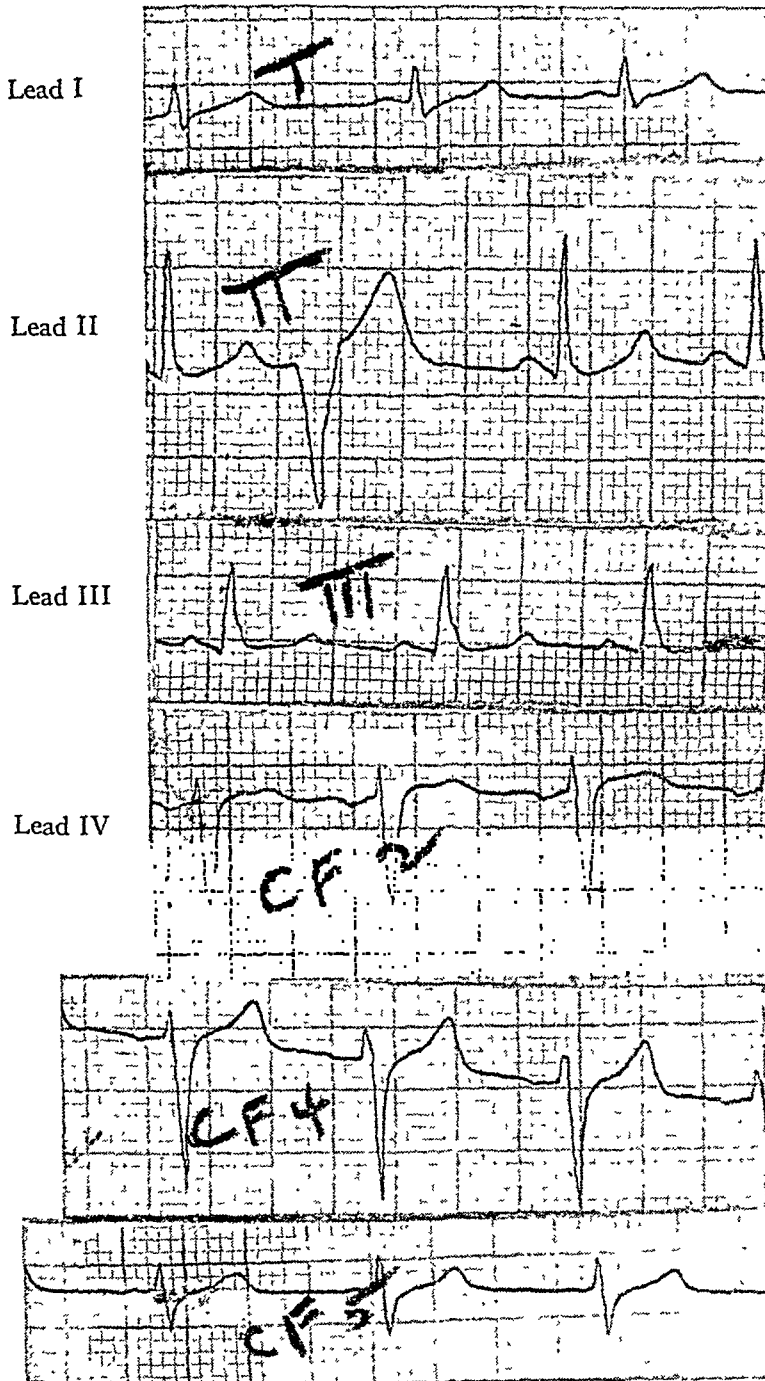


FIG. 2. Electrocardiogram taken four and one-half hours after the tracing shown in figure 1. Sinus rhythm is now present with a rate of 88. Note the marked shift of the axis back to normal, in itself strongly pointing to pulmonary embolism.

with a case of paroxysmal tachycardia in an apparently normal individual is likely to overlook this possibility. The high index of suspicion essential to the diagnosis of many cases of pulmonary embolism must include the paroxysmal arrhythmias. Approximately 300 beats per minute has been considered the upper limit at which the human heart can pulsate. Lyon, in reporting a rate of 313 in a four and one-half week old infant in 1937, reviewed the literature on excessively rapid rates.<sup>13</sup>

gard to the third factor, no single constant abnormality of the blood has been found which can be held responsible in all cases. In the subject of this report local trauma must be considered since the patient was a chronic alcoholic and since he gave a history of playing football with his children for a month prior to his attack. However, he could recall no instance of trauma. Venous stasis may have played a rôle in a patient who occasionally slept cramped in the back seat of his automobile after an alcoholic debauch. In view of the fact that extensive



FIG. 4. Chest roentgenogram three days after attack. A reticular density is present in the outer portion of the mid-right lung, suggesting multiple small emboli.

venous thrombosis has been reported in some cases of primary atypical pneumonia with high cold or autoagglutinin titers and in view of the fact that venous thrombosis is thought to be more common in the spring and winter months when respiratory infections are frequent and more common in the northern clinics than in the southern, an autoagglutinin titer was run one week after admission.<sup>16, 17</sup> The titer was 1 : 80 (4 plus, 3 plus, 2 plus, 1 plus), the end point being determined by the presence of macroscopic clumping. Although 1 : 80 is not a very high titer,

in ice water for one to two minutes. No unusual color change was noted. However, it was noted that, whereas the temperature of the hands of two controls returned promptly to normal, the patient's hand which had been immersed in ice water was distinctly cooler than his other hand one half hour later, and some of the fingers were distinctly cooler than others. We feel that no definite significance can be attached to this.

### SUMMARY

1. A case of pulmonary embolism in an active apparently healthy young adult is reported. The high index of suspicion essential to the diagnosis of many cases of pulmonary embolism must include the paroxysmal arrhythmias even in apparently healthy individuals.

2. The ventricular rate of 300 to 315 beats per minute is, we believe, the fastest recorded in a human heart beyond infancy.

3. The possible etiologic significance of cold or autoagglutinins in this case is briefly discussed.

### BIBLIOGRAPHY

1. ALLEN, E. V., BARKER, N. W., and HINES, E. A.: *Peripheral vascular diseases*, 1946, W. B. Saunders Co., Philadelphia, Pa.
2. BARKER, N. W.: Primary idiopathic thrombophlebitis, *Arch. Int. Med.*, 1936, lviii, 147.
3. BAUER, G.: Venous thrombosis, *Arch. Surg.*, 1941, xliii, 462.
4. BRIGGS, J. B.: Recurring phlebitis of obscure origin, *Bull. Johns Hopkins Hosp.*, 1905, xvi, 228.
5. DETAKATS, G., and FOWLER, E. F.: The problem of thrombo-embolism, *Surgery*, 1945, xvii, 153.
6. FLEISCHNER, F., HAMPTON, A. O., and CASTLEMAN, B.: Linear shadows in the lung, *Am. Jr. Roentgenol. and Rad. Therapy*, 1941, xlvi, 610.
7. HAMPTON, A. O., and CASTLEMAN, B.: Correlation of postmortem chest teleoroentgenograms with autopsy findings with special reference to pulmonary embolism and infarction, *Am. Jr. Roentgenol. and Rad. Therapy*, 1940, xliii, 305.
8. HAMPTON, A. O., PRANDONI, A. G., and KING, J. T.: Pulmonary embolism from obscure sources, *Bull. Johns Hopkins Hosp.*, 1945, lxxvi, 245.
9. HOMANS, J.: Pulmonary embolism due to quiet venous thrombosis, *New England Jr. Med.*, 1943, ccix, 309.
10. JORPES, J. E.: Origin and physiology of heparin, *Ann. Int. Med.*, 1947, xxvii, 361.
11. KATZ, L. N.: *Electrocardiography*, 1946, Lea & Febiger Co., Philadelphia, Pa.
12. KING, J. T.: Personal communication.
13. LYON, J. L.: Excessively rapid heart rates, *Jr. Am. Med. Assoc.*, 1937, cviii, 1393.
14. MEILMAN, E., and DAVISON, S.: Pulmonary embolism of non-cardiac and non-post-operative origin, *Jr. Mt. Sinai Hosp.*, 1944, ii, 164.
15. MURNAGHAN, D., MCGINN, S., and WHITE, P. D.: Pulmonary embolism with and without cor pulmonale, *Am. Heart Jr.*, 1943, xxv, 573.
16. OCHSNER, A.: Intravenous clotting, *Surgery*, 1945, xvii, 240.
17. RENNER, W. F., and MCSHANE, J. R.: The rôle of autoagglutinins in hemolytic anemias, *South. Med. Jr.*, 1947, xl, 973.
18. WHITE, P. D.: *Heart disease*, 1946, The Macmillan Co., New York, N. Y.

eral of the lower ribs showed sclerotic changes and the left costophrenic sinus was obliterated. Intravenous pyelography was negative except for a large oval filling defect in the floor of the bladder presumed to be due to an enlarged prostate. Barium enema and gastrointestinal series were essentially negative.

On July 18 an acid phosphatase of 12.0 G.U. and on August 1, one of 10.2 G.U. were reported. A diagnosis of carcinoma of the prostate with extensive bony metastases was made and the patient was started on pituitary irradiation as an experimental procedure. From July 31 to August 19, the patient received 3,000 roentgens delivered by cross-firing through three fields to the pituitary gland. The patient failed to improve. He complained of increasing pain in the hips and low back. On August 28, weakness of the legs was noted. By the September 2, a marked paraparesis of the lower extremities and an absence of pain perception corresponding to a level of D-8 had developed. In addition, marked hyperreflexia at the knees and ankles with ankle clonus and positive Babinski signs bilaterally were found. Lumbar puncture performed at L 4-5 showed considerable block. As can be seen from figure 1, there was a prompt rise in spinal fluid pressure on applying abdominal pressure but practically

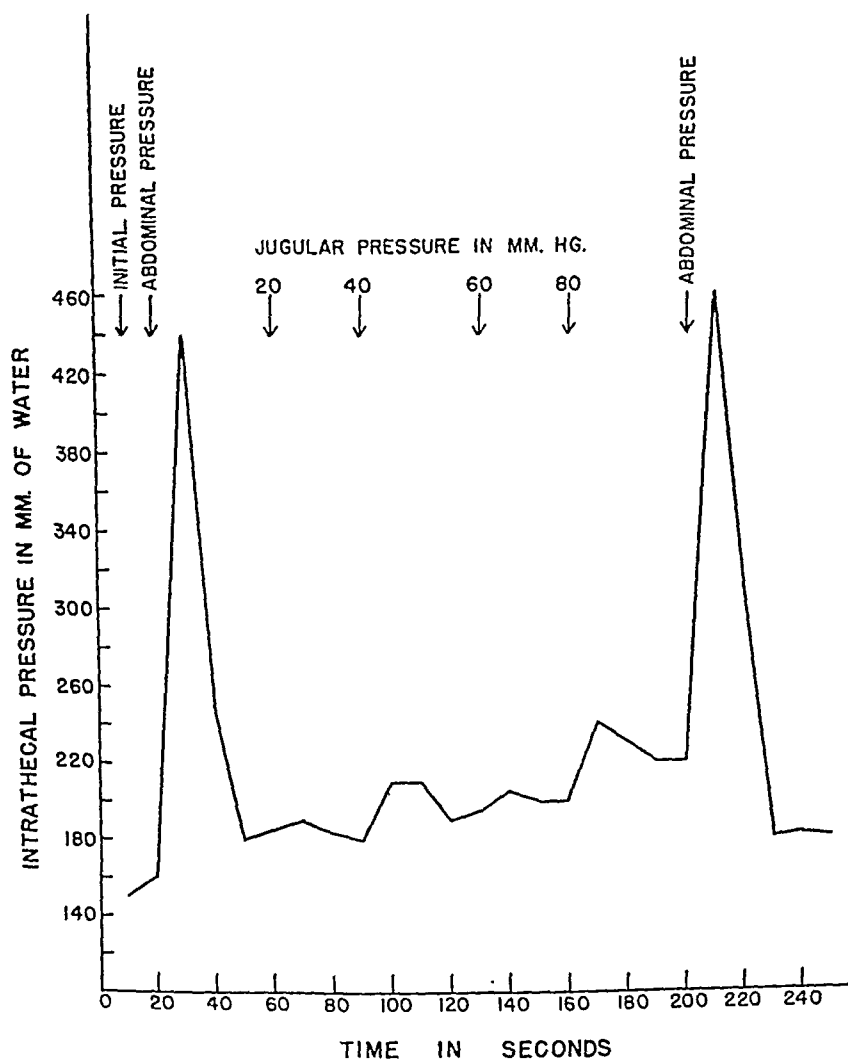


FIG. 1. September 3, 1947. Incomplete block prior to stilbestrol therapy. Spinal fluid manometrics measured with a water manometer and pressure applied by a sphygmomanometer with the cuff around the neck.

of well-being. The patient could stand but not walk unassisted. Ankle clonus and the positive Babinski persisted. On digital rectal examination there seemed to be a decrease in the size of the prostate. The patient was discharged on October 30, 1947. He was seen on November 5, 1947 and continued to be improved.

### DISCUSSION

The diagnosis of prostatic malignancy was based on the physical characteristics of the gland, the fairly typical osteoblastic metastases and acid phosphatase values above 10 units. The striking therapeutic response to estrogenic therapy and fall in the acid phosphatase values to normal supports the diagnosis. Although other conditions can give small increases in serum acid phosphatase levels, a value greater than 10 units is considered to be diagnostic of prostatic carcinoma.<sup>9</sup>

The pathogenesis of the paraplegia seems to be fairly clear. The clear cut evidence of a spinal fluid block without collapse of any of the vertebral bodies indicates that a soft tissue mass was compressing or invading the spinal cord. That this mass was metastatic from the prostate is supported by the considerable symptomatic relief, the open manometrics and return of spinal fluid protein to normal, with stilbestrol therapy.

TABLE I  
Pertinent Laboratory Data before and after Stilbestrol Therapy

	Alkaline Phosphatase Bodansky Units	Acid Phosphatase Gutman Units	Spinal Fluid Protein
7/18/47	16.8	12.0	170 mg. %
8/ 1/47	16.6	10.2	
8/28/47	Onset of Paraplegia		
9/ 4/47			
9/ 5/47	Stilbestrol Therapy Started		31 mg. %
9/29/47	17.7	0.2	
10/13/47	22.8	1.7	
10/14/47			

The time relations and chemical changes indicated in the above table suggest that the relief of the neurologic symptoms came about as a direct result of an inhibiting effect of stilbestrol on the tumor growth in the spinal canal.

Clarke and Viets<sup>10</sup> reported a very similar case with objective evidence of relief of a spinal fluid obstruction. As far as we know this is the second time that objective evidence of relief of a block within the spinal canal by hormonal therapy has been demonstrated. Of greater importance, however, is the palliative effect obtained. In this instance, a patient with advanced and widespread cancer, with severe pain, completely bed-ridden and paralyzed from the waist down, was enabled to leave the hospital free of pain and able to move his legs.

### SUMMARY

A case of paraplegia secondary to metastases from a carcinoma of the prostate is reported. Relief of symptoms and of a spinal fluid block occurred after administration of stilbestrol. The importance of palliation in this type of case is stressed.



Out-Patient Dispensary for thyrotoxicosis and thyrotoxic heart disease since April 1943. Three courses of thiouracil had been administered during this time with a reduction in basal metabolism and temporary improvement in cardiac function. On April 24, 1946 the patient had developed a mild leukopenia during one of the courses of thiouracil and was given 5 mg. folic acid orally three times a day in an attempt to combat it. She took both thiouracil and folic acid for two weeks. When, however, a maculopapular erythematous and pruritic rash appeared over her anterior chest wall and the extensor surfaces of both forearms, she discontinued the folic acid. Within 36 hours the pruritus disappeared and the skin rash had begun to clear even though she was still taking thiouracil. Later the thiouracil was discontinued since the leukopenia persisted and the thyrotoxic symptoms had abated. On April 3, 1947 thiouracil therapy was reinstituted, 0.2 gram three times a day because of recurrent thyrotoxic manifestations. On April 14, 1947 she noted a severe sore throat and an itching maculopapular rash over the arms and shoulders. She discontinued the thiouracil, the rash began to clear but the throat became progressively more painful.

The patient's past history did not reveal any suggestion of allergic tendencies until about three years before admission. At this time she developed recurrent generalized maculopapular eruptions which she attributed to the ingestion of tomatoes, pork or oranges, to contact with woolen blankets, many common soaps and most face powders. During a previous hospitalization she had developed dermatitis following the administration of phenobarbital and an erythematous pruritic rash and shortness of breath shortly after the administration of nembutal and aspirin.

The patient was acutely ill, her temperature was 104° F. and her pharynx was fiery red, edematous and covered with purulent exudate particularly over the tonsils. She had difficulty in swallowing, moderate trismus, and mild cardiac failure with auricular fibrillation. The white blood cell count was 2000 and the differential count 96 per cent lymphocytes and 4 per cent monocytes. The bone marrow showed 9 per cent myeloblasts but no more mature granulocytes. The erythrocyte series was essentially normal and megakaryocytes were present in normal numbers.

During the first week her temperature ranged between 101 and 104°. Penicillin and general supportive measures were ineffective in controlling the throat infection. Since the patient's course was steadily downward and since she showed no evidence of recovery of myeloid elements in the peripheral blood, all types of reputed bone marrow stimulants were given consideration. Folic acid was selected because there had been no reports of hypersensitivity reactions following its administration even though the evidence from the literature and our own experience did not indicate that it would be effective in this type of toxic granulocytopenia.<sup>2</sup> She was given one dose of 50 mg. of synthetic folic acid intravenously on April 24, 1947. There was no objective reaction to this initial injection but the patient stated later that she had noted slight flushing of the face and dizziness. On the following day a second dose of 50 mg. synthetic folic acid was administered intravenously. Immediately after the injection had been completed the patient suddenly became dyspneic, orthopneic, and extremely anxious. She sat up in bed, grasped her chest, and complained of severe substernal oppression. Her face became fiery red, then a livid purple. The pulse rate became extremely rapid (170 to 190 beats per minute) and could not be palpated at the wrist. Her respirations increased to 40 per minute. Blood pressure readings were not taken. The extreme dyspnea and orthopnea lasted about five minutes. Thereafter breathing became easier and orthopnea gradually disappeared. After 10 minutes the patient was able to lie back in bed and the cyanosis of the face had decreased.

Two days following this reaction and again 16 days later intradermal skin tests were carried out with the original solution of folic acid (No. 1) which had produced the reaction and similar material from a second stock bottle of folic acid (No. 2).

3. DOAN, C. A.: Folic acid (synthetic *L. casei* factor), an essential panhematopoietic stimulus. Experimental and clinical studies, *Am. Jr. Med. Sci.*, 1946, ccxii, 257.
  4. SPIES, T. D., VILTER, C. F., KOCH, M. B., and CALDWELL, M. H.: Observations in the antianemic properties of synthetic folic acid, *South. Med. Jr.*, 1945, xxxviii, 707.
  5. VILTER, C. F., VILTER, R. W., and SPIES, T. D.: The treatment of pernicious and related anemias with synthetic folic acid. I. Observations on the maintenance of a normal hematologic status and on the occurrence of combined system disease at the end of one year, *Jr. Lab. and Clin. Med.*, 1947, xxxii, 262.
- 

## DIAGNOSTIC FEATURES OF SPLENIC CYSTS WITH CASE REPORT AND REVIEW OF THE LITERATURE \*

By ARTHUR A. FISCHL, M.D., F.A.C.P., and JEAN PAPPS, M.D.,  
*Jamaica, L. I., N. Y.*

SPLENIC cysts occur infrequently in the human body. They were first mentioned by Andral<sup>1</sup> in 1829 in an autopsy report. Pemberton,<sup>2</sup> in a review of splenectomies at the Mayo Clinic, found four cysts in 800 cases. Sweet<sup>3</sup> more recently reviewed the literature and observed 148 cases of all varieties of cysts up to 1941. This low incidence is no doubt the cause of our paucity of knowledge regarding the clinical features. After reviewing the literature and comparing the essential findings of our case with those reported, we were impressed, however, with the remarkable similarity of the clinical and roentgenological pictures of splenic cysts. The diagnostic features are usually quite evident and afford a basis for a preoperative diagnosis. Discussion of the findings in the case here reported will serve as a general review of this subject.

### CLASSIFICATION

Several classifications of cysts have been outlined. Of these many are confusing and offer little aid to the clinician. McClure and Altmeier<sup>4</sup> divide them into true and false cysts. The true cysts have a specific secreting membrane either epithelial, endothelial or parasitic in nature. The false cysts have a dense hyaline fibrous tissue or a layer of condensed splenic tissue. The contents of the latter may be hemorrhagic, serous, inflammatory or degenerative. Lubarsch<sup>5</sup> divides them into lymphatic cysts with clear fluid, hemorrhagic cysts with bloody contents, and dermoid cysts with sebaceous substance. Paul<sup>6</sup> classifies them into hydatid; multiple serous cysts, usually associated with polycystic disease of the kidney; and single or dermoid, epidermoid, serous or blood cysts.

A histological classification has little to offer. Some writers will classify cysts according to contents, others according to etiology, and still others depend

\* Received for publication April 2, 1947.

From the Medical Service, Queens General Hospital, Dr. James R. Reuling, Director.

to the left shoulder. She was placed on sulfa drugs and penicillin by her local physician, but as the swelling persisted hospitalization was advised.

The past history was essentially negative except for a normal delivery two years previously. Family history was non-contributory.

Physical examination revealed a well-developed and nourished young girl, complaining of pain in the left lower chest and avoiding all motion. Positive findings were limited to the lower thorax and abdomen. There was slight diminution of breath



FIG. 2. Displacement of stomach to right by cyst of spleen.

sounds in the left base posteriorly and a diffuse swelling presented itself anteriorly in the left upper quadrant, which seemed soft and cystic. The outlines of the spleen and liver were not palpable. Moderate tenderness was elicited over the mass, which was about half the size of a grapefruit.

Laboratory studies revealed a normal leukocyte and differential count on three occasions, with 3,400,000 red cells and 8 gm. of hemoglobin. Serologic test for syphilis, blood proteins, urea nitrogen, cephalin flocculation, and alkaline phosphatase

Post-operatively the patient did well. The platelet count was followed for a week post-operatively, rising to a high of 212,000 on the seventh day.

The pathological report by Dr. A. Angrist noted the following: "Specimen consisted of a spleen weighing 610 gm. There was an incision into a loculated cyst filled with thick bloody fluid. The capsule was smooth, dark red in color and contained several hard grayish calcified zones. On section the greater part of the spleen was



FIG. 4. Displaced left kidney to the right of the vertebral column.

made up of loculated large cystic areas lined by a calcified tissue. The impression was that we were dealing with a splenic cyst with a connective tissue wall that showed fibrosis, atheromatosis and slight calcification."

#### DISCUSSION

The etiology of splenic cysts is unknown, though several independent factors are suspected. The presence of these tumors in women of childbearing age has

just under the left costal margin are significant. The presence of pain depends on the size of the mass. A large one may cause the patient to complain of a heavy dragging pain; a smaller one may be less disturbing. The mass usually is soft and cystic. The spleen may or may not be outlined, again depending on the size of the mass. The presence or absence of fever is another problem which offers no help. If the cyst is of the inflammatory variety a febrile reaction will obtain. The presence of a fixed left diaphragm with diminished breath sounds is characteristic. The splenic mass displaces the immediately surrounding structures, notably the left diaphragm, the stomach, and the splenic flexure and transverse colon. Pancreatic and ovarian cysts may offer a problem but they do not offer resistance to the left costal margin. Ovarian cysts may be traced into the pelvis, whereas splenic cysts enlarge, transversely. The large leukemic spleen also grows down towards the pelvis and we do not see the spreading of the ribs and the involvement of the left diaphragm. These clinical findings, if considered with the roentgen visualizations, make the diagnosis obvious.

Roentgenologically, a splenic mass growing anteriorly and under the costal margin causes visceral displacement, and elevates the left diaphragm to impair the latter's motion. The barium-filled stomach is displaced to the right, the colon is pushed down and to the right. The left kidney may also be displaced downward. Calcification occurs frequently enough in these splenic tumors to have been commented upon by Bachman,<sup>10</sup> Gallagher,<sup>11</sup> Jamison,<sup>12</sup> Shawan,<sup>13</sup> and Snoke<sup>14</sup> in their case reports. Ostro and Makover<sup>15</sup> feel that any spleen that grows downward and anteriorly will not displace the neighboring organs as will a splenic cyst. Benton<sup>16</sup> feels that downward displacement of the splenic flexure is almost pathognomonic of large cysts of the spleen.

The laboratory is of no help in the differential diagnosis except in a negative fashion.

Therapy is specific. All cases are amenable to surgery and usually do very well.

#### SUMMARY

1. A case report of a patient with a splenic cyst is given because of the relative infrequency of the condition.
2. The etiology of splenic cysts is still obscure.
3. The diagnostic features of a palpably enlarged tumor, paucity of symptoms, occasional calcification, pathognomonic roentgenological findings are stressed.

#### BIBLIOGRAPHY

1. ANDRAL, G.: *Precis d'anatomie pathologique*, Paris, 1829, ii, 432.
2. ROBERSON, F.: Solitary cysts of spleen, *Ann. Surg.*, 1940, iii, 848-850. (Pemberton J. de J., discussor of paper.)
3. SWEET, R. H.: Single true cysts of the spleen, *New England Jr. Med.*, 1943, ccxxviii, 705-710.
4. McCLURE, R. D., and ALTMEIER, W. A.: Cysts of spleen, *Ann. Surg.*, 1942, cxvi, 98-102.
5. LUBARSCH, O.: Die Zysten der Milz, *Im Handbuch der Speziellen Path., Anat. und Histol.*, J. Springer, Berlin, 1927, i, 718-728.
6. PAUL, MILROY: Cysts of spleen, *British Jr. Surg.*, 1943, xxx, 336-339.
7. FOWLER, R. H.: Cystic tumors of the spleen, *Surg., Gynec. and Obst.*, 1940, lxx, 213-223.
8. DeLEE, J. B.: Principles and practice of obstetrics, 1930, W. B. Saunders & Co., Philadelphia, p. 106.

time Weingarten's article arrived in the middle East, and neoarsphenamine was then employed with dramatic success.

In 1945 another case was reported by Hirst and McCann <sup>4</sup> in another naval officer serving in the Pacific area, who suddenly developed severe asthma accompanied by headaches. He had never been in India and his overseas duty had been in Central America and the central and south Pacific islands. His asthmatic symptoms had their onset two years previously in Samoa. He was found to have a leukocytosis of 15,000 cells per cu. mm. with a hypereosinophilia up to 72 per cent, which later rose to 82 per cent. The sputum was loaded with eosinophiles. No parasites could be found. His response to neoarsphenamine therapy was again dramatic, five doses four days apart resulting in prompt and complete cure.

Van der Sar and Hartz <sup>5</sup> in 1945 reported their experiences with cases of tropical eosinophilia observed in Curaçao, and conclude that they have demonstrated the relationship between this disease and filariasis since they were able to demonstrate microfilariae in a biopsied lymph node from a typical case of tropical eosinophilia.

Apley and Grant <sup>6</sup> in 1945 reported on five cases observed in England in servicemen invalided back from the Middle East, all of whom promptly responded to arsenical therapy. They further discussed the possible relationship between Loeffler's syndrome, tropical eosinophilia, periarteritis nodosa, and bronchial asthma, which they classify together under the term "E P syndrome," meaning eosinophilia with pulmonary infiltration.

In 1946 Irwin <sup>7</sup> reported two additional cases of tropical eosinophilia originating in the southwest Pacific which also responded to arsenical therapy. He calls attention to the possibility of this being caused by filariasis, as suggested by Van der Sar and Hartz, inasmuch as both of his patients had spent considerable time in an area where *Wuchereria bancrofti* is prevalent. However, repeated examinations of the blood at all hours revealed no microfilaria and the biopsies from muscle, lymph node, and bone marrow showed no filariae although both patients had positive skin test reactions to *Dirofilaria immitis* antigen. He pointed out, however, that false positives are common in the use of this antigen.

It has thus been established that arsenical compounds are specific in the treatment of tropical eosinophilia and that prompt and complete recovery follows their use. As far as we can determine it has never been effective in the other conditions characterized by marked eosinophilia. The effect of penicillin in tropical eosinophilia has not to our knowledge been reported previously. It is for this reason that we decided to test its action in this disease.

#### CASE REPORT

The patient, a 23 year old Marine sergeant, was admitted to a naval hospital on February 11, 1947, complaining of nocturnal cough, progressive loss of weight amounting to 28 pounds during the past six months, and general malaise. He stated that he had been perfectly well and healthy until after his return from the western Pacific (Japan) in March, 1946. One month later he noted the onset of a deep nocturnal cough productive of a moderate amount of thick, tenacious, dark-colored sputum. Although the cough was present to some extent during the day it usually became worse after going to bed and would awaken him around 2 a.m. He would usually vomit after a particularly severe coughing spell, often being unable to retain his break-

zation he lost six additional pounds of weight. Temperature, pulse, and respiration remained normal. The white cell count increased to 17,750 with 61 per cent eosinophiles. An electrocardiogram made on February 17 revealed no evidence of myocardial damage, with normal sinus rhythm, rate 75 per minute, P-R interval 0.18 second, and T waves upright in all leads. The Davidsohn test was negative as were all routine febrile agglutination tests. Dark-field examinations of the blood serum were negative for parasites. Stool cultures were negative and sputum cultures on Sabouraud's medium showed no growth. The erythrocyte sedimentation rate was now 13 mm. in 60 minutes. On February 22 a large lymph node 25 mm. in diameter was removed from the left axilla. Upon microscopic examination, the lymph node architecture was well preserved. The capsule was thin and showed some blood vessel congestion. The follicles showed marked hyperplasia of the germinal centers with much lymphoblastic activity. The mature lymphocytes about the follicles were lined up in almost concentric rings. The peripheral sinuses were dilated and in some areas contained lymphocytes. Reticulo-histiocytic elements showed moderate hyperplasia, and an occasional large macrophage containing brown pigment granules could be seen. Large numbers of plasma cells and polys were present. No evidence of malignancy was noted and the histologic appearance of the node was consistent with the picture seen in tropical eosinophilia. Pathologically the histological diagnosis was chronic lymphadenitis with reticulo-endotheliosis.

The following skin tests were employed: (1) *Dipilidium caninum*, 0.5 c.c., intradermally, was positive, showing erythema, pseudopodia, and enlargement of the wheal to one-half inch within 15 minutes. The control remained negative. (2) *Trichinella spiralis*, 1:10,000, 0.02 c.c., intradermally was negative. (3) Coccidioidin, intradermally, gave positive results. (4) *Dirofilaria immitis*, 1:10,000, produced an immediate positive reaction in 30 minutes, the control remaining negative. (5) P.P.D. tuberculin test (first strength) was negative. (6) Skin tests for 36 common allergens, including air-borne pollens, foods, and animal dander were all negative.

On February 22 the erythrocyte sedimentation rate was 13 mm. in 60 minutes, hemoglobin 14.5 gm. (103 per cent), leukocytes 17,450, 49 per cent of which were eosinophiles. The platelet count was 378,000. Chest roentgenograms revealed some clearing of the hilar markings as compared with previous films. Roentgen-rays of the skull, long bones, and muscles were reported as negative for soft tissue calcifications which might represent encysted parasites. The patient now weighed 132 pounds. The basal metabolic rate was plus 13 per cent. The patient was treated with intramuscular adrenalin-in-oil and oral benadryl which gave some relief of his severe asthmatic symptoms. After seven days of this treatment a concurrent decrease in symptoms, leukocytosis and eosinophiles to 30 per cent occurred. This was probably coincidental.

Commencing on March 4, 100,000 Oxford units of penicillin were given intramuscularly every three hours to a total of 8,000,000 units. By the end of the course of penicillin, the eosinophilic count had increased slightly. The patient continued to gain weight and was free of symptoms. No changes were seen in the lung fields by weekly roentgen-rays.

Following the cessation of penicillin therapy, two weeks were allowed to elapse, but no significant change in the blood picture occurred, the leukocyte count remaining about the same and the eosinophiles ranging between 20 per cent and 30 per cent. Finally, on March 22 a course of six injections of neoarsphenamine intravenously was commenced. At first there was a steady decline in the eosinophilia from 30 per cent to 11 per cent, then it temporarily rose as high as 17 per cent, finally subsiding to within normal limits. The case could not be followed further, as the patient was discharged from the Service and returned to his home. When last seen in mid-April, he was gaining weight, symptom-free, and his blood counts were still normal.

lin, in none of them. For this reason, we administered penicillin to this case, and as far as we could determine it had absolutely no effect.

The weight of evidence in regard to this group of diseases will doubtlessly continue to be that they are of an allergic nature. Rich<sup>15, 16</sup> has advanced the hypothesis that the lesions of periarteritis nodosa are the result of hypersensitivity, and in 1942 he reported five autopsies on patients who had serum sickness before death. In all of them he was able to demonstrate the characteristic lesions of periarteritis nodosa. He later demonstrated similar vascular lesions in two patients following reactions to sulfonamide therapy, and in the following year Rich and Gregory<sup>17</sup> succeeded in producing similar lesions experimentally in rabbits by sensitizing them to horse serum. This appears to be additional evidence in support of Apley and Grant's classification of these four diseases under the "E-P syndrome."

In regard to filariasis being a factor, whether allergic or infective, in tropical eosinophilia, it is known that after patients are removed from endemic areas they become symptom-free because the filaria are unable to multiply until they undergo further passage in mosquitoes, and hence die out. However, reliable therapeutic agents against filariasis are not known. The diagnosis is usually made without demonstrating the filaria and laboratory tests are seldom helpful.<sup>18</sup>

It is our opinion, unsupported by concrete evidence, but nevertheless in accordance with the conclusions of Van der Sar and Hartz, that this patient acquired a minimal infestation with *Wuchereria bancrofti* during his stay in Samoa. Following the death of the parasites upon his return to a temperate climate he developed the typical signs and symptoms of tropical eosinophilia. This failed to respond to treatment with penicillin but promptly subsided following the administration of neoarsphenamine.

#### SUMMARY

A case is presented in which the clinical history, course and laboratory findings were consistent with a diagnosis of tropical eosinophilia.

The patient had been stationed in Samoa and gave a positive skin reaction to *Dirofilaria immitis*. This appears to be additive evidence to support the hypothesis of Van der Sar et al. and others, that tropical eosinophilia may be due to filarial infestation.

Penicillin is of no therapeutic value in this disease although the empirical use of organic arsenicals is amazingly effective.

#### BIBLIOGRAPHY

1. WEINGARTEN, R. J.: Tropical eosinophilia, *Lancet*, 1943, i, 103-105.
2. EMERSON, KENDALL: Tropical eosinophilia, *U. S. Nav. Med. Bull.*, 1944, xlii, 118-123.
3. PARSONS-SMITH, B. G.: Tropical eosinophilia, *Lancet*, 1944, i, 433-434.
4. HIRST, W. R., and McCANN, W. J.: Tropical eosinophilia, *U. S. Nav. Med. Bull.*, 1945, xliv, 1277-1281.
5. VAN DER SAR, A., and HARTZ, H.: The syndrome, tropical eosinophilia, and microfilaria, *Am. Jr. Trop. Med.*, 1945, xxv, 83-96.
6. APLEY, J., and GRANT, G. H.: Tropical eosinophilia, *Lancet*, 1945, i, 812-813.
7. IRWIN, J. W.: Tropical eosinophilia, *Ann. Int. Med.*, 1946, xxv, 329-339.
8. BROWN, H. W.: Personal communication.
9. HUNTINGTON, R. W., JR.: Skin reactions to *Dirofilaria immitis* extract, *U. S. Nav. Med. Bull.*, 1945, xliv, 707-717.



The primary renal defect responsible for hyperchloremia was clearly shown to be an inadequate tubular reabsorption of water in the face of continued electrolyte retention.<sup>1</sup> The serum bicarbonate level was not depressed, unlike the hyperchloremia found after administration of calcium chloride or other acid-producing salts.<sup>2</sup> Despite serum chloride levels of 140 to 160 milliequivalents per liter (normal 100 to 110), the urine, though always of considerable volume in the hyperchloremic stage, showed a very low fixed chloride concentration. Similarly, in one patient it was shown that 97 per cent of the chloride in the glomerular filtrate was reabsorbed by the tubules, while only 90 per cent of the water was reabsorbed. Glomerular filtration was 30 per cent of the expected normal rate.

Autopsied cases showed a severe toxic tubular nephrosis with necrosis and thrombosis of adjacent interlobular veins and minimal glomerular damage. The brains examined showed widely scattered foci of gliosis, edema and hemorrhage.

The extreme degree of hyperchloremia without acidosis was considered to be clinically almost unique among renal disease and among other causes of electrolyte disturbance. A comparable hyperchloremia, however, has been produced experimentally in dogs by Winkler and his co-workers.<sup>3, 4</sup> By injecting hypertonic saline solution they produced chloride levels up to 193 milliequivalents per liter and found a generalized intracellular dehydration as well as a loss in intracellular potassium. The cerebral type of death in these dogs, without cardiorenal failure, was somewhat reminiscent of Luetscher's cases of hyperchloremia in man. There was no evidence for the existence of a critical level of either sodium or chloride in dogs.

Even since the original report of hyperchloremia in sulfathiazole nephrosis, the syndrome has not been widely recognized or reported.\* It therefore seemed worthwhile to report a case which followed the oral administration of small doses of sulfadiazine.

#### CASE REPORT

A 23 year old single unemployed Italian man entered the Peter Bent Brigham Hospital on Dec. 14, 1945, in coma.

At the age of seven he developed chronic osteomyelitis of the right femur, treated by open drainage, with fractures of the same bone and recurrence of the infection at 10 and 13 years of age. At 10 years of age he also had pyelitis. Up to the age of 17, he was crippled by an increasing shortening and bowing of this leg, requiring a lift and brace. At the age of 17, six years before the present illness, he had had a supracondylar osteotomy at the Massachusetts General Hospital to correct the deformity. Sulfanilamide was given prophylactically, 3 to 6 gm. daily for six days. Nine days postoperatively a staphylococcus infection recurred at the operative site requiring two courses of seven days each of sulfanilamide, 5 to 6 gm. daily, and three days of sulapyridine, 4 gm. daily. Urine, white blood count and hemoglobin remained normal throughout the three month hospital course without drug fever or rash.

Recovery followed without further recurrence and he was left with only a slight limp from a one inch shortening. As a devotee of boxing and a professional sparring partner, he received frequent blows to the head but no known concussion. He was considered by his family physician to be an inadequate person, never able to hold a

\* Maisel, Kubik and Ayer<sup>5</sup> reported a case of encephalopathy following sulfathiazole therapy with an elevated non-protein nitrogen which fell to normal terminally, without progressive oliguria, and yet with a progressively fatal coma. At autopsy, both renal and cerebral lesions were found, quite similar to those reported by Luetscher and Blackman. Clinically and pathologically the resemblance was close enough to suggest that the hyperchloremic syndrome may have been present, although no serum chloride determination was reported.

high power field in the unspun sediment. Urine guaiac positive, stool guaiac negative. Hematocrit 51.5 per cent, hemoglobin 17.2 gm. per cent, corrected sedimentation rate 0.9 mm. per minute, white blood cell count 6,700 with 66 per cent polymorphonuclears, 14 per cent band forms, 16 per cent lymphocytes and 4 per cent eosinophiles. Blood urea nitrogen 104 mg. per cent, serum non-protein nitrogen 170 mg. per cent, total protein 8.4 mg. per cent, fasting blood sugar 65 mg. per cent, serum carbon dioxide combining power 22 millimoles per liter, serum chloride 140 milliequivalents per liter, icteric index 15, sulfadiazine level 0. Electrocardiograms and skull films were normal. A chest film was normal except for prominence of the left ventricle. Two blood cultures and a urine culture were negative.

*Hospital Course:* An intake of over 4,000 c.c. of salt-free intravenous glucose lowered the chloride level from 140 to 113 milliequivalents per liter and the hematocrit from 51.5 to 43 per cent within the first 36 hours. The high fluid intake was continued, however, for an additional 12 hours until the report on the rapid fall in serum chloride had been received and evaluated. By 48 hours after admission the patient had received a total of 7,000 c.c. of salt-free fluids, dehydration had disappeared, a gain in weight of 3 kg. was noted, and he looked slightly edematous. Fluid therapy was therefore suspended. A few hours later his temperature suddenly rose to 105 degrees, the pulse to 144 and the respirations to 60, and the latter were deep as well as rapid. Emergency chemical determinations showed a rise in the blood urea nitrogen to 140 mg. per cent and a fall in the serum carbon dioxide combining power to 18.9 millimoles per liter. He was given 80 c.c. of a one molar sodium lactate solution and 20 gm. of salt-free albumin in 1,000 c.c. of dextrose and water. The temperature then promptly fell to 101.6°, the pulse to 100, the respirations to 40, and the serum carbon dioxide combining power rose to 21.9 millimoles per liter within a few hours. On the third day oliguria progressed gradually to a state of anuria so that intravenous fluid therapy was again suspended. Generalized edema was now obvious with pitting in the sacral region. Finally, the blood pressure fell below 100 mm. of mercury and the respirations became very shallow while the temperature rose again to 105°. There were no signs of pulmonary edema at any time, however, and an electrocardiogram and repeated examinations of the heart at this point were normal. Despite 4 units of plasma and the usual stimulants, he died 78 hours after admission, in shock, with a terminal hyperpyrexia of 108.2 degrees.

*Autopsy:* The body was that of a normally developed and well nourished white man. There was a moderate degree of pitting of the lower extremities and sacral region. The heart was not remarkable. In the lungs, large irregular areas of consolidation, proved by microscopic examination to be confluent bronchopneumonia, were found scattered throughout all the lobes. The liver appeared normal. The right kidney weighed 260 gm. and the left kidney 350 gm. They were of the usual shape. The arrangement of the ureters and renal vessels at the pelvis was normal. The renal capsules were thin and could be stripped with ease leaving smooth, firm, pale reddish-brown surfaces. Vertical sections of each kidney showed the cortex and medulla to be clearly demarcated. The cortex of each kidney measured from 1.0 to 1.2 cm. in width. The tubular striations of the papillae were clearly seen. The cut surfaces appeared edematous and moist and the cortex protruded above the capsule. The calyces and pelves and ureters were normal in shape and thickness. Numerous pinpoint hemorrhages were found in the pelvis and papillae. No significant gross findings were noted in any of the other organs. Permission for examination of the brain was not granted.

*Microscopic Studies:* Sections of kidney were fixed in Zenker's fluid and in 10 per cent formalin and stained with eosin-methylene blue, hematoxylin-eosin, Kossa's silver stain for calcium, Turnbull's blue stain for iron, and benzidine stains. The most striking renal lesions involved the tubules. Many tubules were dilated and the

degree for iron. These casts were present for the most part in the intercalated segments of the distal convoluted tubules, but were occasionally found in the loops of Henle and in the proximal portion of the collecting tubules. The next type of cast in order of frequency was a pale, slightly basophilic, homogeneous cast and these casts were interpreted as being made up of protein. These casts did not react with the iron, benzidine or Kossa's silver stain for calcium. The third type of cast was

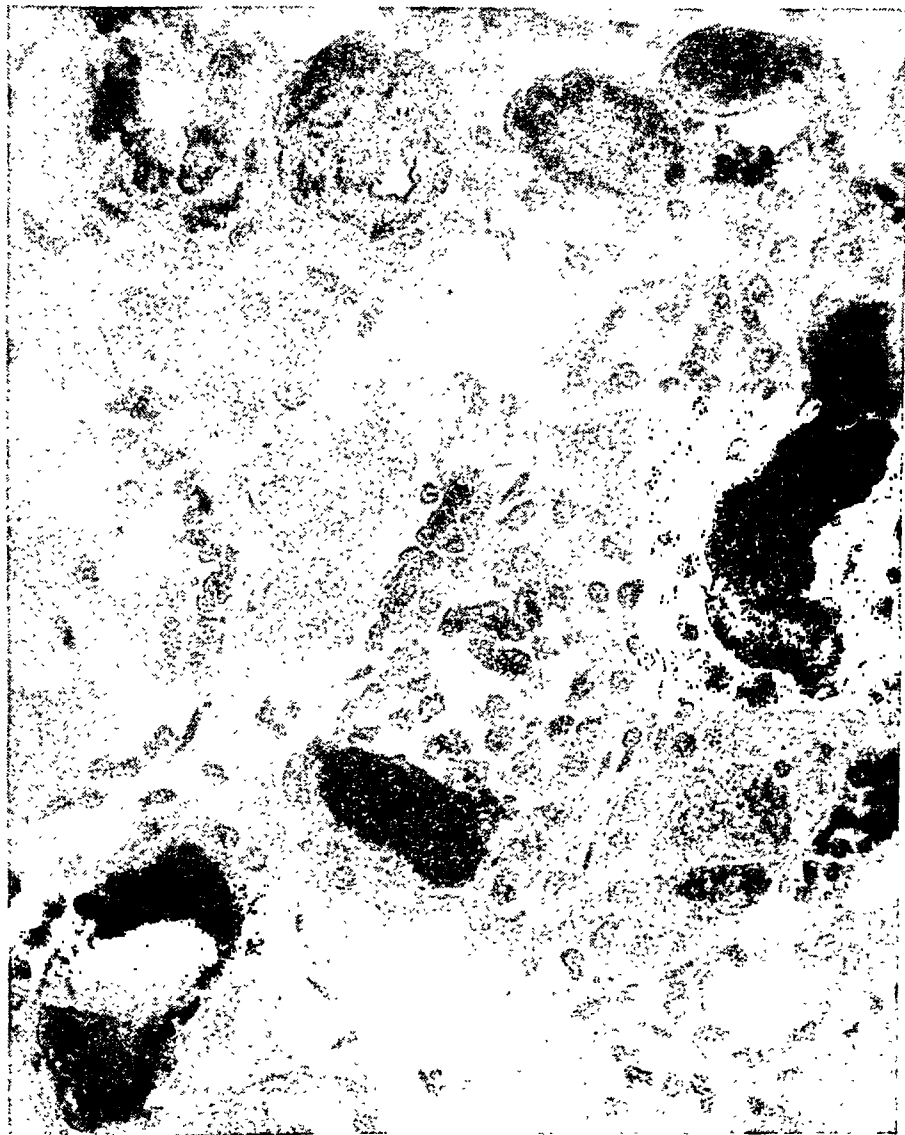


FIG. 2. High power photomicrograph showing the character of the refractile tubular casts. Eosin-methylene blue stain.

made up of finely granular material which stained reddish-brown with the eosin-methylene blue stain. This material had the appearance of hemosiderin and this was confirmed by the iron stains.

It should be noted that in addition to the above findings small collections of reddish-brown pigment suggesting hemosiderin and giving a positive reaction to the iron stains were found in the epithelium of some of the tubules.

approached a terminal stage of the disease. With increasing oliguria, excessive fluids given once dehydration had been corrected could only have tended to form edema fluid. Generalized edema appeared in this case despite the fact that fluids administered contained no salt and despite the probability that the total body electrolyte content was never increased.\* This edema, by including the kidney as found at autopsy, may have contributed to the eventual total renal failure. In the brain, edema may have aggravated the encephalopathy as suggested by the terminal hyperpyrexia of 108.2°.

A high salt-free fluid intake is therefore probably indicated only while hyperchloremia is actually present. Once hyperchloremic dehydration is controlled the fluid intake should depend upon the urine output. It has been repeatedly emphasized that in the usual toxic nephrosis without hyperchloremia, a high fluid intake will not force an oliguric or anuric kidney to increase its urine output and will only tend to add the further complication of pulmonary or generalized edema.<sup>12, 13</sup>

Finally, generalized depletion of intracellular potassium may well be an important pathophysiological factor in these cases, as found by Elkinton, Winkler et al. in dogs.<sup>3, 4</sup> The possible benefit of potassium replacement therapy should be emphasized.

*Alkalinization in Sulfonamide Therapy:* In preventing renal damage from sulfonamides, the value of routine adjuvant alkali therapy is debatable. The various renal lesions to be considered are outlined in table 1. Of these lesions, only Group I, the crystallurias, are preventable by the use of alkali. Sulfonamides and their esters are relatively insoluble in an acid urine and the crystals can cause irritation, hematuria and obstruction at any point from the tubules to the bladder. Sodium bicarbonate, or sodium r-lactate, given in sufficient dosage of 12 to 22 gm. daily has been shown to decrease or eliminate crystalluria by raising the pH of the urine to at least 7.5 at which point the sulfonamides are quite soluble.<sup>13-15</sup> However, even obstructive anuria with uremia, the most serious complication of crystalluria, may be readily treated by ureteral lavage or nephrostomy, usually with complete recovery.<sup>11</sup> An adequate fluid intake and avoidance of overdosage by determinations of the blood sulfonamide level will also help greatly to prevent these reactions.

The more serious sulfonamide nephropathies, toxic nephrosis<sup>16-19</sup> and those due to hypersensitivity,<sup>20-22</sup> often lead to irreversible renal damage if not a direct fatality (table 1, Groups II and III). These lesions are apparently unrelated to crystalluria, however, and their incidence is not decreased by the use of alkali, judging from a review of the larger series of experimental and clinical studies.<sup>16-19, 22-26</sup> On the contrary, Earle has shown that sodium bicarbonate greatly increases the tubular excretion of sulfamerazine, lowering the blood level so that a higher dosage is required and thus increasing the total exposure of the tubular cells to this toxic agent.<sup>27</sup>

\* Patients with renal disease show a pathological tendency to divert salt and fluid from the blood into the tissues even with a body electrolyte content which is usually normal or low. For example, most nephritics are unable to develop the transient hydremia of approximately 4 per cent which is seen in normals after the ingestion of hypertonic saline solution.<sup>10</sup> Such salt solutions are taken up almost immediately by the tissues to form edema fluid in the nephritic, without even a transiently detectable hydremia. This fact might explain why even salt-free fluids greatly in excess of the urine output could alone carry a patient with renal insufficiency from a state of hyperchloremic dehydration over to one of generalized edema at a normal or low serum chloride level.

hydration has been controlled the volume of fluid intake should usually be promptly restricted, depending upon the urine output, in order to avoid over-treatment to the point of causing generalized edema.

Potassium replacement therapy may well be indicated, judging from the evidence of generalized intracellular potassium deficiency in experimental hyperchloremia in dogs.

This case once more illustrates the potential dangers of sulfonamide therapy, even in small oral doses, and the ineffectiveness of routine alkali administration in preventing a fatal sulfonamide nephrosis.

#### ADDENDUM

Since this report was completed, two additional cases of hyperchloremia and hypernatremia without marked acidosis, have been observed at the Peter Bent Brigham Hospital. Both cases showed a toxic encephalopathy. One followed the use of sulfathiazole, and was also referred from a psychopathic hospital, having shown initially a predominance of psychotic symptoms. The other case occurred following severe gastrointestinal hemorrhage, and will be reported in detail by Merrill and his associates, among a series of patients treated by means of a modified Kolff artificial kidney.<sup>37</sup>

#### BIBLIOGRAPHY

1. LUETSCHER, J. A., and BLACKMAN, S. S., JR.: Severe injury to kidneys and brain following sulfathiazole administration: high serum sodium and chloride levels and persistent cerebral damage, *Ann. Int. Med.*, 1943, xviii, 741-756.
2. GAMBLE, J. L.: Extracellular fluid, a lecture syllabus, Department of Pediatrics, Harvard Medical School, 1942.
3. WINKLER, A. W., ELKINTON, J. R., HOPPER, J., JR., and HOFF, H. E.: Experimental hypertonicity: alterations in body water and cause of death, *Jr. Clin. Invest.*, 1944, xxiii, 103-109.
4. ELKINTON, J. R., and WINKLER, A. W.: Transfer of intracellular potassium in experimental dehydration, *Jr. Clin. Invest.*, 1944, xxiii, 93-102.
5. MAISEL, B., KUBIK, C. S., and AYER, J. B.: Encephalopathy, nephrosis and renal granuloma following sulfonamide therapy; case with autopsy, *Ann. Int. Med.*, 1944, xx, 311-326.
6. KINSEY, R. E.: Psychosis due to sulfonamides, *Ann. Int. Med.*, 1943, xix, 795-798.
7. FISHER, J. H., and GILMOUR, J. R.: Encephalomyelitis following administration of sulfanilamide with note on histological findings, *Lancet*, 1939, ii, 301-305.
8. ROSEMAN, E., and ARING, C. D.: Encephalopathy associated with sulfamethylthiazole therapy, *N. E. Jr. Med.*, 1941, ccxxiv, 416-420.
9. BLANKENHORN, M. A.: Multiple peripheral neuritis occurring with sulfonamide therapy, *Ann. Int. Med.*, 1944, xx, 423-430.
10. LITTLE, S. C.: Nervous and mental effects of sulfonamides, *Jr. Am. Med. Assoc.*, 1942, cxix, 467-474.
11. STYRON, C. W., and LEADBETTER, W. F.: The treatment of anuria, *N. E. Jr. Med.*, 1944, ccxxx, 721-728.
12. KUGEL, V. H.: Management of acute toxic nephrosis, *Am. Jr. Med.*, 1947, iii, 188-205.
13. FOX, C. L., JR., JENSEN, O. J., JR., and MUDGE, G. H.: Prevention of renal obstruction during sulfadiazine therapy, *Jr. Am. Med. Assoc.*, 1943, cxxi, 1147-1150.
14. GILLIGAN, D. R., GARB, S., WHEELER, C., and PLUMMER, N.: Adjuvant alkali therapy in the prevention of renal complications from sulfadiazine, *Jr. Am. Med. Assoc.*, 1943, cxxii, 1160-1165.
15. PENNA, O. J., and CHRISTOPHER, F.: Alkalization of urine during sulfonamide therapy, *Jr. Am. Med. Assoc.*, 1946, cxxx, 1067-1069.

## EDITORIAL

### AMINOPTERIN IN THE TREATMENT OF ACUTE LEUKEMIA

THE inhibition of the biological activity of an essential metabolite by compounds which are structurally related to it is now a well known phenomenon. The underlying principles believed to be involved and their importance in the study of fundamental metabolic processes have previously been discussed in this journal.<sup>1</sup> Folic acid (pteroyl glutamic acid) and its specific antagonists constitute one of the most carefully studied examples of this relationship. By an antagonist in this sense is meant a substance which will inhibit the growth of *Lactobacillus casei* in a suitable culture medium containing barely adequate amounts of folic acid, but whose inhibitory action can be overcome by adding more folic acid to the medium. Within appropriate quantitative limits, a similar antagonism can be demonstrated in experimental animals.

Stimulated by the observations of Lewisohn and associates that *L. casei* fermentation factor (containing pteroyltriglutamic acid) frequently caused regression of certain breast cancers in mice, Farber et al.<sup>2</sup> administered this material to human subjects with various types of inoperable malignant tumors. In certain cases it seemed to be beneficial in causing subjective improvement and diminution in size of the tumor. When given to cases of acute leukemia, however, it seemed to accelerate and aggravate the process. This led them to try the effect of folic acid antagonists, and in 1948<sup>3</sup> they reported obtaining temporary remissions in 10 of 16 cases of acute leukemia. These observations aroused widespread interest, and folic acid antagonists have been employed on an experimental basis in the treatment of acute leukemia in many clinics. Several different compounds have been used with more or less effect, but at present the most potent and most extensively employed is aminopterin (4-aminopteroyl glutamic acid).

Farber<sup>4</sup> has since summarized the results obtained by his group. Of about 60 children treated for three weeks or longer, somewhat over 50 per cent showed clinical or hematological improvement or both. Reports of other observers have in general confirmed Farber's observations that remissions may be obtained, but the frequency of such remissions has varied greatly in different clinics.

Dameshek and his associates<sup>5</sup> have studied a series of 34 cases, chiefly

<sup>1</sup> SACKS, M. S.: Biologic competition between structurally related compounds, Editorial, Ann. Int. Med., 1949, xxx, 867-870.

<sup>2</sup> FARBER, S., et al.: The action of pteroyl glutamic conjugates on man, Science, 1947, cvi, 619-621.

<sup>3</sup> FARBER, S., et al.: Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl glutamic acid (aminopterin), New England Med. Jr., 1948, ccxxxviii, 787-793.

<sup>4</sup> FARBER, S.: Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer, Blood, 1949, iv, 160-167.

<sup>5</sup> DAMESHEK, W.: The use of folic acid antagonists in the treatment of acute and subacute leukemia, Blood, 1949, iv, 168-171.

quickly follows. If a relapse occurs, resumption of a full dose may bring about further remissions. Patients have been maintained in reasonably good condition in this way for many months, and one case for nearly two years. Eventually, however, either they fail to respond to aminopterin or grave toxic symptoms necessitate terminating treatment, the disease progresses, and death ensues. No case has been cured. Aminopterin seems to be ineffective in chronic myeloid leukemia.<sup>7, 11</sup>

Aminopterin is a potent and very dangerous drug, and its effects are by no means limited to the hemopoietic tissues. Toxic manifestations are frequent and often severe. In many cases they are unavoidable if an effective dose is administered. One of the commonest is an ulcerative stomatitis which is often but not invariably associated with a leukopenia. Manifestations of a gastroenteritis are also frequent. More serious are profuse hemorrhages, especially from the nose and gastrointestinal tract, which may be uncontrollable. Leukopenia is common, and there may be an extreme granulocytopenia with increasing anemia and thrombocytopenia, associated with hypoplasia of the marrow which may be irreversible. Cutaneous eruptions have been described in severe cases. Among occasional minor manifestations may be mentioned alopecia and deafness.

Ulcerations of the buccal mucous membranes and hemorrhages are common manifestations of the disease and do not necessarily contraindicate treatment with aminopterin. In patients who are under treatment, however, it may be difficult to determine whether such symptoms are referable to the disease or to the drug.

Individual susceptibility to aminopterin varies, and the dose has to be adjusted for each case. Severe toxemia may appear abruptly. It often subsides, however, if aminopterin is stopped promptly and suitable treatment administered (folic acid, transfusion, antibiotics).

There are obvious difficulties in interpreting the results of treatment in these cases. Spontaneous remissions occur occasionally in acute leukemia. The frequency with which they occur is not known precisely, but Diamond's<sup>4</sup> estimate of 10 per cent is probably a maximum figure. Furthermore spontaneous remissions as complete and long lasting as those described in some of the reported cases are quite rare. There can be little doubt that aminopterin has favorably influenced the course of the disease and that its effect is much more definite than that of the other procedures which have been previously employed.

It is equally evident, however, that aminopterin is a highly unsatisfactory therapeutic agent. Its action is unpredictable, and it is effective in only a minority of the cases. Its effect is temporary only, and no cure, nothing more than a transient remission can be hoped for. It causes serious toxic reactions, and some degree of such action must be anticipated if effective quantities are given. In many cases these reactions are prohibitively severe.

<sup>11</sup> BERMAN, L., et al.: Use of a folic acid antagonist in chronic leukemia, *Am. Jr. Clin. Path.*, 1949, xix, 127-133.

## REVIEWS

*Conditioned Reflexes and Neuron Organization.* By JERZY KONORSKI. 267 pages; 14.5 × 22.5 cm. Cambridge University Press, London; Macmillan Co., New York. 1948. Price, \$4.00.

This book is written by a former pupil of Pavlov's working in Poland, whose laboratory was destroyed and whose researches were interrupted by the war. The intention of the author is shown by his dedication to Pavlov and Sherrington: "... In the hope that this work will do something to bridge the gulf between their respective achievements."

It is not a book for the amateur or general reader, but is only for those who are already deeply steeped in either Pavlovian tradition or neurophysiological work.

The author takes up in detail the basic concepts of Pavlov which he considers need thorough revision, for example internal inhibition, irradiation, induction, summation, sleep, nomenclature. He feels that the material contributed by Pavlov is of enormous importance, not only in its special field but for the advancement of more strictly neurophysiological research. He claims that his concept of higher nervous activity is in harmony with general physiology of the nervous system and the neuron theory. The elaboration of a conditional reflex he thinks depends upon new functional connections in the brain and the multiplication of synapses. Unless there is repetition of excitation within a certain period the synaptic connections undergo atrophy. Internal inhibition consists in a formation of used synaptic connections of inhibitory character. The author feels that in spite of the erroneous nature of some of Pavlov's theories, the great physiologist has enormously enriched our knowledge of the nervous system and the ability to explore its intricacies in the future through the method of study of the conditional reflex.

W. HORSLEY GANTT

*Modern Practice in Psychological Medicine.* Edited by J. R. REES, M.D. 488 pages; 17 × 25 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper and Bros., New York. 1949. Price, \$10.00.

This book is a collection of papers by a group of outstanding British and Canadian psychiatrists and psychologists. The topics covered are chapter headings of what one would expect in a textbook of psychiatry. As one can expect, there is some unevenness of excellence and considerable overlapping of topics. On the whole, however, the book is timely, up-to-date and of value as a general introduction to physicians who wish to know more about the emotional aspects of their patients. The point of view on the whole is conservative and practical. The editor, Dr. J. R. Rees, writes a chapter on Psychotherapy which is full of sound and useful advice to the general practitioner.

H. W. N.

*Heart: A Physiologic and Clinical Study of Cardiovascular Diseases.* By ALDO A. LUISADA, M.D. 653 pages; 25.5 × 19 cm. The Williams and Wilkins Company, Baltimore. 1948. Price, \$10.00.

The simple but comprehensive title of this book is well chosen, for its contents are not confined to *diseases* of the heart. With a background of over 20 years of investigative and clinical cardiology, the author has a unique and intimate knowledge with which to endow his work, and a wealth of cardiac physiology is included. There



## BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Advances in Pediatrics—Volume IV.* Editorial Board: S. Z. LEVINE, Cornell University Medical College, New York; ALLAN M. BUTLER, Harvard Medical School, Boston; L. EMMETT HOLT, JR., New York University, College of Medicine, New York, and A. ASHLEY WEECH, University of Cincinnati, College of Medicine, Cincinnati. 316 pages; 24 × 15.5 cm. 1949. Interscience Publishers, Inc., New York. Price, \$6.50.

*Arterial Hypertension: Its Diagnosis and Treatment.* 2nd ed. By IRVINE H. PAGE, M.D., and ARTHUR CURTIS CORCORAN, M.D., Research Division of the Cleveland Clinic Foundation, Cleveland. 400 pages; 21 × 14.5 cm. 1949. The Year Book Publishers, Inc., Chicago. Price, \$5.75.

*Bone and Joint Radiology.* By EMERIK MARKOVITS, M.D., Formerly Scientific Collaborator of the Central Radiologic Institute of the General Hospital (Holzknecht-Institute), Vienna, etc. 446 pages; 26 × 18 cm. 1949. The Macmillan Company, New York. Price, \$20.00.

*Clinical Diagnosis by Laboratory Examinations.* 2nd ed. By JOHN A. KOLMER, M.S., M.D., Dr.P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry of Temple University, etc. 1212 pages; 25.5 × 17 cm. 1949. Appleton-Century-Crofts, Inc., New York. Price, \$12.00.

*The Development of Gynaecological Surgery and Instruments: A Comprehensive Review of the Evolution of Surgery and Surgical Instruments for the Treatment of Female Diseases from the Hippocratic Age to the Antiseptic Period.* By JAMES V. RICCI, M.D., Clinical Professor of Gynaecology and Obstetrics, New York Medical College, etc. 594 pages; 27 × 18.5 cm. 1949. The Blakiston Company, Philadelphia. Price, \$12.00.

*Differential Diagnosis of Chest Diseases.* By JACOB JESSE SINGER, M.D., F.A.C.P., F.C.C.P., Medical Director of the Rose Lampert Graff Foundation, Beverly Hills, etc. 344 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, \$7.50.

*Digitalis and Other Cardiotonic Drugs.* 2nd ed. By ELI RODIN MOVITT, M.D., Chief of Medicine, Veterans Administration Hospital, Oakland, California, etc. 245 pages; 24.5 × 16 cm. 1949. Oxford University Press, New York. Price, \$5.75.

*Diseases of the Aorta: Diagnosis and Treatment.* By NATHANIEL E. REICH, M.D., F.A.C.P., Associate in Medicine, Long Island College of Medicine, etc. 288 pages; 24 × 16 cm. 1949. The Macmillan Company, New York. Price, \$7.50.

*Die Dystrophie.* By PROFESSOR DR. MED. HEINRICH BERNING. 197 pages; 24.5 × 17.5 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, Halbleinen DM 18.—

*Functional Localization in Relation to Frontal Lobotomy, Being the William Withering Memorial Lectures Delivered at the Birmingham Medical School, 1948.* By JOHN F. FULTON, O.B.E., M.D., D.SC., LL.D. (Birm.). 140 pages; 21 × 13 cm. 1949. Oxford University Press, New York. Price, \$3.00.

# COLLEGE NEWS NOTES

## ELECTIONS TO FELLOWSHIP AND ASSOCIATESHIP

### AMERICAN COLLEGE OF PHYSICIANS

NOVEMBER 13, 1949

(*FELLOWS, FULL CAPITALS: Associates, lower case*)

SALVADOR ACEVES .....	Mexico, D. F.
FRANK MARVIN ADAMS .....	Hot Springs Nat'l Park, Ark.
LEYLAND JOHN ADAMS .....	Montreal, Que., Can.
WRIGHT ADAMS .....	Chicago, Ill.
Clarence Mendel Agress .....	Beverly Hills, Calif.
Elmer Alpert .....	New York, N. Y.
GEORGE JOHN ANDAY .....	Chicago, Ill.
CHARLES HENRY ARMENTROUT .....	Asheville, N. C.
LEONARD MAX ASHER .....	Beverly Hills, Calif.
Allie Kearney Atkinson .....	Great Falls, Mont.
Joseph Gordon Barrow .....	Atlanta, Ga.
HYMAN ELIHU BASS .....	New York, N. Y.
Jere Marklee Bauer .....	Ann Arbor, Mich.
George Leonard Baum .....	Milwaukee, Wis. (V.A.)
EDWARD HORTON BENSLEY .....	Montreal, Que., Can.
EUGENE SYDNEY BERESTON .....	Baltimore, Md.
KARL HENRY BEYER, JR. ....	Bala-Cynwyd, Pa.
Anthony Andrew Bianco .....	New York, N. Y.
Hylan Arthur Bickerman .....	Forest Hills, N. Y.
Maxwell Jacob Binder .....	Los Angeles, Calif. (V.A.)
CECIL CLINTON BIRCHARD .....	Montreal, Que., Can.
James Bell Black, Jr. ....	Richmond, Va.
HERRMAN LUDWIG BLUMGART .....	Boston, Mass.
JOHN JAMES BOEHRER .....	Minneapolis, Minn.
WILLIAM PIERCE BOGER .....	Upper Darby, Pa.
Eli Leroy Borkon .....	Carbondale, Ill.
GEORGE ARTHUR BOYLSTON .....	Portland, Ore.
E(mory) James Brady .....	Denver, Colo.
C(HARLES) H(ENRY) HARDIN BRANCH ...	Salt Lake City, Utah
John Grierson Brazier .....	Omaha, Nebr.
Samuel Henry Brethwaite .....	Summit, N. J.
I. JAY BRIGHTMAN .....	Albany, N. Y.
(GEORGE) MALCOLM BROWN .....	Kingston, Ont., Can.
Herbert Rutherford Brown, Jr. ....	Rochester, N. Y.
James Cushing Brudno .....	Quincy, Mass.
HEINRICH GEORGE BRUGSCH .....	Boston, Mass.
JOSEPH BUDNITZ .....	Pittsfield, Mass.
Samuel Simon Burden .....	Elkins Park, Pa.
William Champlin Burrage .....	Portland, Maine
Irving Frederick Burton .....	Detroit, Mich.
Ewald William Busse .....	Denver, Colo.
Maston Kennerly Callison .....	Memphis, Tenn.
John Dodd Cameron .....	Defiance, Ohio

Murray Franklin .....	Iowa City, Iowa
JOSEPH THEODORE FREEMAN .....	Philadelphia, Pa.
Harold Aaron Friedman .....	Rochester, N. Y.
Murray Marcus Friedman .....	Santa Fe, N. M.
HAROLD FRUCHTER .....	Long Island City, N. Y.
CHARLES WATSON FULLERTON .....	Montreal, Que., Can.
Jabez Galt .....	Dallas, Tex.
E(dward) Philip Gelvin .....	New York, N. Y.
JACQUES GENEST .....	Montreal, Que., Can.
Joseph Gennis .....	New Rochelle, N. Y. (V.A.)
Charles Everett Gerson ..	Dayton, Ohio
James Alan Longmore Gilbert .....	Moose Jaw, Sask., Can.
Sidney Gilbert .....	Flushing, N. Y.
John Stuart Gilson .....	Great Falls, Mont.
Charles Harold Gingles .....	M. C., U. S. Army
Samuel Glassman .....	New York, N. Y. (V.A.)
Henry Goebel, Jr. ....	Bethlehem, Pa.
Jacob Goldberg .....	Castle Point, N. Y. (V.A.)
MORTON LOUIS GOLDHAMER .....	Cleveland, Ohio
Morris Irving Goldin .....	Detroit, Mich.
Michael Louis Gompertz .....	New Haven, Conn.
IRVING ISRAEL GOODOF .....	Auburn, Maine
Alvin Joseph Gordon .....	New York, N. Y.
John Edgar Gordon .....	Lebanon, Pa. (V.A.)
Philip Morris Gottlieb .....	Philadelphia, Pa.
Alexander Gotz .....	Ann Arbor, Mich.
SAMUEL U. GREENBERG .....	New York, N. Y.
Laurence Abraham Grossman .....	Nashville, Tenn.
Charles Michael Gruber, Jr. ....	Drexel Hill, Pa.
JOHN HINER GUSS .....	Staunton, Va.
GERALD WINTER HALPENNY .....	Montreal, Que., Can.
Henry Edward Hamilton .....	Iowa City, Iowa
Courtney Norfleet Hamlin .....	Rockford, Ill.
George Wesley Hammel .....	El Dorado, Kans.
Laura Hare .....	Indianapolis, Ind.
John D. Hartigan .....	Omaha, Nebr.
Eslie Hartman .....	Chicago, Ill.
George Harvey, Jr. ....	Jackson, Miss.
JOSEPH PAUL HARVEY .....	Youngstown, Ohio
Elmer Russell Hayes .....	Minneapolis, Minn.
ELWYN LINDLEY HELLER .....	Pittsburgh, Pa.
Lowell Lawrence Henderson .....	Urbana, Ill.
Frederick Harrison Hesser .....	Iowa City, Iowa
Albert Heyman .....	Atlanta, Ga.
JOSEPH SPURGEON HIATT, JR. ....	McCain, N. C.
Samuel Gaston Hibbs .....	Tampa, Fla.
Eugene Hildebrand .....	Great Falls, Mont.
GLENN IVAN HILLER .....	Highland Park, Mich.
John Hendricks Hodges .....	Philadelphia, Pa.
Martin Mandell Hoffman .....	Montreal, Que., Can.
George Hollander .....	Philadelphia, Pa.
Irving Nathan Holtzman .....	Brooklyn, N. Y.
Ralph E. Homann, Jr. ....	Los Angeles, Calif.

David Lehr .....	New York, N. Y.
Stephen Howard Leslie .....	New York, N. Y.
Eli Allen Leven .....	Rochester, N. Y.
Herbert Melville Levenson .....	Framingham, Mass.
Matthew Levine .....	New York, N. Y.
Samuel Marrel Levit .....	Philadelphia, Pa.
William Likoff .....	Philadelphia, Pa.
JOSEPH FRANCIS LINSMAN .....	Beverly Hills, Calif.
EMANUEL WILLIAM LIPSCHUTZ .....	Brooklyn, N. Y.
Lester Lipson .....	Monticello, N. Y.
Jesse Cone Lockhart .....	Peoria, Ill.
HARRY JOSEPH LOWEN .....	New York, N. Y.
John Morgan Lyon .....	Englewood, Colo.
WILLIAM CHARLES MACDONALD .....	St. Louis, Mo.
Thomas Keith MacLean .....	Vancouver, B. C., Can.
Harold Haze Macumber .....	Chichasha, Okla.
Frank Joseph Manganaro .....	Kirkwood, Mo.
Sydney Gerald Margolin .....	New York, N. Y.
Jerome David Markham .....	Richmond, Va.
THOMAS WILLIAM MATTINGLY .....	M. C., U. S. Army
EDWARD MATZGER .....	San Francisco, Calif.
Edward Schuyler McCabe .....	Philadelphia, Pa.
Marcus Denney McDivitt .....	Pittsburgh, Pa.
Douglas Francis McDowell .....	Santa Barbara, Calif.
Charles Joseph McGee .....	Brockton, Mass.
FRANK BARTLETT McGLONE .....	Denver, Colo.
Arthur Joseph McSteen .....	Greensburg, Pa.
Edward Idel Melich .....	Largo, Fla. (V.A.)
Patterson Morris Menlowe .....	McKeesport, Pa.
Arthur Jesse Merrill .....	Atlanta, Ga.
John Putnam Merrill .....	Waban, Mass.
William Josef Messinger .....	New York, N. Y.
John Wright Middleton .....	Galveston, Tex.
Ernest Boyd Millard, Jr. ....	Rochester, N. Y.
Solomon Samuel Mintz .....	Philadelphia, Pa.
HOWARD SCOTT MITCHELL .....	Montreal, Que., Can.
Frank Corbin Moister .....	Hanover, N. H.
ROLLEN WAYNE MOODY .....	Denver, Colo.
J(oseph) Lloyd Morrow .....	Passaic, N. J.
Paul Vanderhoff Morton .....	San Jose, Calif.
Jack Duane Myers .....	Durham, N. C.
SAMUEL MYERSON .....	Bay Pines, Fla. (V.A.)
Max J. Nareff .....	Jamaica, N. Y.
Maurice Nataro .....	Louisville, Ky. (V.A.)
John Robert Neefe .....	Philadelphia, Pa.
Jack Nelson .....	New York, N. Y.
JAMES DAVID NELSON .....	Spartanburg, S. C.
Carl Robert Newman .....	Redwood City, Calif.
Robert H. Nickau .....	Jacksonville, Fla.
Joseph Henry Nicholson .....	Lawrence, Mass.
Joseph Mazarin Oppenheim .....	Detroit, Mich.
James Archer Orbison .....	M. C., U. S. Army

ROGER GRAHAM SIMPSON .....	San Francisco, Calif.
John Clark Slaughter, Jr. ....	Evansville, Ind.
(FREDERICK) McIVER SMITH .....	Montreal, Que., Can.
Glen T. Smith .....	New York, N. Y.
Maurice Snyder .....	Salina, Kans.
Arnold Stanton .....	Richmond Hill, N. Y.
Louis Wells Staudt .....	Ann Arbor, Mich.
James Milton Steele .....	Jamestown, N. Y.
LAWRENCE IRVING STELLAR .....	Newton Center, Mass.
Edward Amberg Stern .....	Rochester, N. Y.
Marvin Stern .....	Brooklyn, N. Y.
HAROLD STEVENS .....	Washington, D. C.
Chester Pratt Stevenson .....	Fort Logan, Colo. (V.A.)
Herman Hull Stone .....	Oklahoma City, Okla. (V.A.)
THEODORE THADDEUS STONE .....	Chicago, Ill.
Lee Stover .....	Lincoln, Nebr.
Arnold Ferdinand Strauss .....	Norfolk, Va.
Benjamin Hardy Sullivan, Jr. ....	M. C., U. S. Army
CLEMENT JOSEPH SULLIVAN .....	St. Louis, Mo.
JAMES MARION SUTER .....	Abingdon, Va.
Adney Kemple Sutphin .....	Richmond, Va.
Robert Edmund Switzer .....	M. C., U. S. Navy
HENRY JOSEPH TAGNON .....	New York, N. Y.
Charles Conover Talbot .....	Chicago, Ill.
Luther Leonidas Terry .....	U. S. Public Health Service
J(oseph) Edward Tether .....	Indianapolis, Ind.
Morris Edward Thomas .....	Indianapolis, Ind.
Alexander Irwin Thomashow .....	Brooklyn, N. Y.
Charles Waters Thompson .....	Washington, D. C.
Philip Pickering Thompson, Jr. ....	Portland, Maine
Meyer C. Thorner .....	Beverly Hills, Calif.
Henry Harding Tift .....	Macon, Ga.
Philip Murry Tiller, Jr. ....	New Orleans, La.
MARTIN LOUIS TRACEY, SR. ....	Needham, Mass.
Jerome Victor Treusch .....	Beverly Hills, Calif.
Isaac Frank Tullis, Jr. ....	Memphis, Tenn.
James Lyman Tullis .....	Newton, Mass.
Walter Richard Tupper .....	North Hollywood, Calif.
GEORGE CLEVELAND TURNER .....	Chicago, Ill.
David Turnoff .....	Philadelphia, Pa.
Samuel Vaisrub .....	Winnipeg, Man., Can.
WESLEY VAN CAMP .....	Pueblo, Colo.
Paul Anton Van Pernis .....	Grand Rapids, Mich.
Helen D. Van Vactor .....	Indianapolis, Ind.
JOHN ORREN VAUGHN .....	Santa Monica, Calif.
Cristobal Alberto Vicens .....	New York, N. Y.
Leo Joseph Wade .....	University City, Mo.
ELMER GLENN WAKEFIELD .....	Rochester, Minn.
Thomas Franklin Walker, Jr. ....	Great Falls, Mont.
C(HARLES) STEWART WALLACE .....	Ithaca, N. Y.
William Bertalan Walsh .....	Washington, D. C.
William Vincent Walsh .....	North Little Rock, Ark. (V.A.)

forms for rooms will be distributed to all members with the program on or about February 1.

*Admission of Non-Members to the Boston Meeting*

Due to excessively crowded conditions the past two years, partially occasioned by the large number of non-sponsored non-members, and at the urgent demand of members of the College, the attendance of non-members at the Boston Session will be limited to those who are specifically sponsored by letter by members of the College. Such non-members should be sponsored three weeks in advance of the Session through letters to the Executive Office of the College, 4200 Pine Street, Philadelphia 4, Pa. The non-member registration fee, which not only covers admission to the Meeting but entitles the attendant to the proceedings as published in the ANNALS OF INTERNAL MEDICINE, will be \$25.00.

---

CANDIDATES FOR MEMBERSHIP

THE AMERICAN COLLEGE OF PHYSICIANS

Meetings of the Committee on Credentials will be held March 19 and April 15, 1950. Provisions of the By-Laws require that proposals of candidates shall be filed in the Executive Office at least 60 days in advance of action.

---

PROPOSED GRADUATE COURSES

The Advisory Committee on Postgraduate Courses, with the approval of the Board of Regents, has presented the following tentative schedule of courses for the future. It must be understood that the directors and the institutions must be consulted before final announcements may be made. Furthermore, dates will be announced a little later. It is proposed to publish the Postgraduate Bulletin for the Spring of 1950 at an early date.

*Spring, 1950, Proposed Courses:*

INTERNAL MEDICINE: University of California School of Medicine, San Francisco; one week; to be scheduled just before the annual meeting of the American Medical Association in June, 1950.

CLINICAL ALLERGY: Roosevelt Hospital, New York, N. Y.; one week.

DISEASES OF THE CIRCULATION: Michael Reese Hospital, Chicago, Ill.; one week.

ELECTROCARDIOGRAPHY: Massachusetts General Hospital, Boston, Mass.; Conger Williams, M. D., Director; one week.

ENDOCRINOLOGY: University of Illinois et al., Chicago, Ill., Willard O. Thompson, M.D., F.A.C.P., Director; one week.

DISEASES OF THE BLOOD VESSELS: Cornell University Medical College, New York, N. Y.; one week.

PHYSIOLOGICAL BASIS OF PSYCHOSOMATIC MEDICINE: Neurological Institute, New York, N. Y.; one week.

*Summer, 1950, Proposed Course:*

CLINICAL ASPECTS OF MALNUTRITION: Hospital de Enfermedades de la Nutricion, Mexico, D. F.; Salvador Zubiran, M.D., F.A.C.P., Director; two weeks, August 14-26, 1950.

*Autumn, 1950 Proposed Courses:*

HEMATOLOGY: Boston, Mass.; William B. Castle, M.D., F.A.C.P., Director; one week.

INTERNAL MEDICINE: University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director; one week.

preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend varies from \$2,200 to \$3,200, according to the obligations of the recipient. Application forms are obtainable through the Executive Secretary of the College, 4200 Pine Street, Philadelphia 4, Pa.

Applications may be filed for the period July 1, 1951-June 30, 1952. All Fellowships for 1950-51 have been assigned.

In accordance with the recommendations of the Committee on Fellowships and Awards, the Board of Regents on November 13, 1949, made the following awards of Research Fellowships to start July 1, 1950:

Edward Harvey Estes, Jr., M.D.; aged 24; a graduate of Emory University School of Medicine, 1947; to work under Dr. James V. Warren, Department of Physiology, Emory University School of Medicine, on the response of the pulmonary vascular bed to hemodynamic alterations in the systemic circuit.

Dalton Jenkins, M.D.; aged 31; a graduate of the University of Colorado School of Medicine, 1943; to work under Dr. George W. Thorn, F.A.C.P., Peter Bent Brigham Hospital, Boston, Mass., on a study of the adrenal hormones on specific metabolic functions, with particular relationship to muscle metabolism.

Edward Howell Lanphier, M.D.; aged 27; a graduate of the University of Illinois College of Medicine, 1949; to work under Dr. Julius H. Comroe, Jr., F.A.C.P., Department of Physiology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., on the investigation of new functional tests of the cardiovascular-pulmonary system.

William Andrew MacIlwaine, M.D.; aged 27; a graduate of the University of Virginia Department of Medicine, 1947; to work under Dr. Byrd S. Leavell, F.A.C.P., University of Virginia Department of Medicine, Charlottesville, Va., to study the effects of various procedures and substances on hemoglobin metabolism in sickle cell anemia.

Cheves McCord Smythe, M.D.; aged 25; a graduate of Harvard Medical School, 1947; to work under Dr. Stanley E. Bradley, Department of Medicine, Presbyterian Hospital, New York, N. Y., on a problem concerned with renal and hepatic physiology as studied by blood flow technics.

William Jape Taylor, M.D.; aged 25; a graduate of Harvard Medical School, 1947; to work under Dr. J. D. Myers, Department of Medicine, Duke University School of Medicine, Durham, N. C., to study the effects of insulin, epinephrine and adrenal cortical substances on the splanchnic glucose, phosphate and potassium intakes and outputs; also to study the effect of parenteral fat on hepatic blood flow and oxygen consumption.

Dr. Edward Harvey Estes, Jr. was selected from the above group of six to be designated as the "Alfred Stengel Research Fellow."

---

#### MISSISSIPPI REGIONAL MEETING REPORT

The second Annual ACP Regional Meeting of the State of Mississippi was held at Jackson, Miss., October 8, 1949, under the Governorship of Dr. John G. Archer, F.A.C.P., of Greenville. Every feature of the program and of the meeting was eminently successful, as attested to by the fact that every member of the College from Mississippi with the exception of four was present. There were 7 members of the College from Tennessee, 3 from Arkansas, and 1 from Louisiana, and among the guests were Dr. William C. Chaney, F.A.C.P., Governor for Tennessee, Dr. A. A. Blair, F.A.C.P., Governor for Arkansas, and Dr. G. W. F. Rembert, F.A.C.P., former Governor for Mississippi. At the reception and banquet in the evening, there were 71 members, guests and wives in attendance, a considerable increase over the attendance at the first Regional Meeting a year ago.

jector for standard slides, a projector for Kodachrome slides, and a sound-motion picture 16 mm. projector. These projectors have been acquired and are of the finest quality, and are now available for all meetings or other events held at the College Headquarters. The gift was accepted with deep appreciation by the Board of Regents at its meeting on November 13, 1949.

---

#### PRESIDENT FITZ BECOMES LIFE MEMBER

Dr. Reginald Fitz, F.A.C.P., President of the American College of Physicians, became a Life Member on November 12, 1949, through a generous subscription to the Endowment Fund. The total life members number 799, of whom 69 are now deceased, leaving a balance of 730.

The Life Membership plan of the American College of Physicians is equitable both to the member and to the College. It affords the member an opportunity of paying his full dues during his productive years and while his income is greatest, and thus avoiding the burden of dues later in life. It, therefore, provides a means for underwriting dues years in advance and of receiving the premium of active membership throughout one's entire life. Members are invited to request the Executive Offices to mail them the folder, "Membership Without Dues," which gives all details.

---

#### COMING EXAMINATIONS, CERTIFYING BOARDS

(1) THE AMERICAN BOARD OF INTERNAL MEDICINE. William A. Werrell, M.D., Assistant Secretary-Treasurer, 1 West Main St., Madison, Wis. Written Examination—once yearly, to be given on 3rd Monday of October. Oral Examination—Chicago, Ill., February 8-9-10, 1950; Boston, Mass., April 13-14-15, 1950; San Francisco, Calif., June 21-22, 23, 1950.

The examination in Boston is given during the week just preceding the Annual Session of the American College of Physicians; the examination in San Francisco is given during the week preceding the annual meeting of the American Medical Association.

Oral examinations in the sub-specialties of Allergy, Cardiovascular Disease, Gastro-enterology and Tuberculosis will be held at the same time and places.

The closing dates for acceptance for all examinations will be January 1, 1950.

(2) THE AMERICAN BOARD OF PEDIATRICS. John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa. Written Examination—under local monitors, Thursday, January 12, 1950 from 2:00 to 4:00 p.m. This is the only written examination scheduled for 1950. Oral Examination—Richmond, Va., February 10-11-12, 1950; Philadelphia, Pa., March 31, April 1-2, 1950; San Francisco, Calif., June 23-24-25, 1950.

---

#### NATIONAL CONFERENCE ON CARDIOVASCULAR DISEASES

A National Conference on Cardiovascular Diseases will be held in Washington, D. C., January 18-20, 1950, under the joint sponsorship of the American Heart Association and the National Heart Institute of the U. S. Public Health Service. This will be the first national conference bringing together physicians, scientists, community service leaders, and members of allied professions to formulate a comprehensive program to combat the nation's leading cause of death.

Dr. Paul D. White, F.A.C.P., Chief Medical Adviser to the National Heart Institute, is Chairman of the Steering Committee.



NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD., PROPOSED \$40,000,000  
CLINICAL CENTER

A clinical center, already in course of construction, for the National Institutes of Health at Bethesda, Md., will be a combined hospital and research institution and will have elaborate medical equipment and basic science laboratories together with hospital facilities for five hundred patients. It will be a fourteen story building, air-conditioned, and will cost \$40,000,000. It is scheduled to be completed by July, 1952.

An auditorium seating 500 will be equipped with television, and some seats will be specially wired for the hard of hearing. The center will be supervised by Dr. R. E. Dyer, Director of the National Institutes of Health. It is said that the Government already has "colonies" of trainees for the center established throughout the country, who are being recruited and trained for particular types of research. Surgeon General Leonard A. Scheele of the Public Health Service states that this is to be a research center and not an institution in competition with private physicians and private hospitals. It is stated further that there will be intimate collaboration between the center and the medical schools of the country.

---

DR. J. ROSCOE MILLER, F.A.C.P., BECOMES 12TH PRESIDENT OF  
NORTHWESTERN UNIVERSITY

On October 26, 1949, Dr. J. Roscoe Miller, F.A.C.P., was installed as 12th President of Northwestern University, and was awarded the honorary degree of doctor of laws. Dr. Miller had been a member of the faculty of Northwestern University for nineteen years and had been Dean of the Medical School since 1941.

---

Dr. William B. Bean, F.A.C.P., Head of the Department of Internal Medicine at the State University of Iowa College of Medicine, Iowa City, was elected Vice President of the Central Society for Clinical Research, at its recent meeting in Chicago.

---

Dr. Theodore R. Van Dellen, F.A.C.P., Chicago, Ill., Assistant Professor of Medicine, Northwestern University Medical School, has been appointed Assistant Dean, succeeding Dr. George H. Gardner, resigned.

---

Dr. Robert F. Pitts, F.A.C.P., Syracuse, N. Y., Professor of Physiology, Syracuse University College of Medicine since 1946, has resigned to become Head of the Department of Physiology and Biophysics and Professor of Physiology at Cornell University Medical College, New York, N. Y., on January 1, 1950. Dr. Pitts was formerly on the faculty at Cornell University. He holds his Ph.D. degree from Johns Hopkins University and his M.D. from New York University. For two years, 1938-40, he was a Fellow of the Rockefeller Foundation.

---

Dr. George Morris Piersol, M.A.C.P., Secretary-General of the ACP, was a guest on the program of the Puerto Rico Medical Association Meeting at San Juan, December 14-18, 1949.

---

Dr. Harold G. Wolff, F.A.C.P., Professor of Neurology and Psychiatry, Cornell University Medical College, delivered an address on "Life Situations, Emotions and Bodily Disease" at the New School for Social Research, New York City, on November 4, 1949.

with dependents), or \$458.88 a month (if single and without dependents). These figures compare with former pay totals of \$417 and \$361, respectively.

A physician or dentist who has acquired sufficient professional experience, and who can meet the other requirements, may be commissioned directly as a captain or higher. A captain's pay, with emoluments, in the Medical and Dental Corps, is now \$546 (with dependents) or \$531 (without dependents), as against \$462 and \$426, respectively. On completion of four years of service, a captain receives regular increases at two-year intervals.

Comparable increases have been made in the higher grades, thus making the financial rewards of military service more commensurate with those of private practice.

---

The Institute for Cancer Research and the Lankenau Hospital Research Institute, Philadelphia, held opening exercises for its new laboratories in Fox Chase on November 16, 1949. There was a program covering a discussion on "Modes of Procedure in Cancer Research," followed by "Open House" and demonstrations by the staffs of the Institutes.

The new laboratories are extensive and represent in facilities and equipment the finest possible setup for cancer research. The staff is being enlarged materially. Both Institutes were organized and have been directed for many years by Dr. Stanley Reimann, F.A.C.P.

---

The Southern Medical Association held its forty-third Annual Meeting in Cincinnati, Ohio, November 14-17, 1949, under the presidency of Dr. Oscar B. Hunter F.A.C.P., Washington, D. C.

---

#### ANOTHER POST-CONVENTION CRUISE TO BERMUDA, FOLLOWING THE BOSTON SESSION, 1950

Following the Annual Session of the American College of Physicians at New York during the Spring of 1949, an official cruise was conducted to Bermuda, occupying a period of approximately one week. Those of the College who went on the cruise were delighted with all the arrangements and the beauties of the islands. Many were disappointed who could not accompany the group.

The Annual Session in Boston comes at a time, April 17-21, 1950, when there are no appropriate post-convention tours available in the New England states, due to the uncertainty of weather and other factors. Consequently, it has been decided to offer again the cruise to Bermuda. Members can take a late afternoon or evening train from Boston on Friday, April 21, arriving in New York, Saturday morning, where they may spend their morning on personal affairs, and board the "Queen of Bermuda" in the early afternoon. The Itinerary is as follows:

- April 22, Sat., 3:00 p.m. Sail from New York; The famous Bays and Skyline, Tea, Dancing in the evening.
- 23, At sea, the Gulf Stream, Movies, Tea, Dancing.
- 24, Bermuda, the beautiful islands. Cruise along the charming North Shore and into Hamilton Harbor, one of the loveliest in the world. Arrive Hamilton at 9 a.m.
- 25, About two and a half days in Bermuda. Opportunity for unusual sight-seeing drives, visits to the Caves and Coral Gardens, shopping, golf, or other diversions.
- 26, Plenty of time today for last minute purchases or drives. Leave Hamilton at 3:00 p.m.

## OBITUARIES

## DR. THOMAS ADDIS

Thomas Addis, M.D., F.R.C.P., F.A.C.P., San Francisco, Calif., died June 4, 1949, at the age of 67. Dr. Addis was born in Scotland, July 27, 1881. He received the degree of M.B., Ch.B. in 1905, from the University of Edinburgh Faculty of Medicine, and thereafter pursued postgraduate work for two years at Berlin and Heidelberg, Germany. He joined the faculty of Stanford University School of Medicine in 1911, and became Professor of Medicine, serving until 1946, when he retired from active teaching. He was a Fellow of the Royal College of Physicians of Edinburgh and received from that organization, in 1942, the Cullen Prize "for the greatest benefit done to practical medicine in the previous four years." He was a member of the Association of American Physicians, National Academy of Sciences, the American Society for Clinical Investigation, and had been a Fellow of the American College of Physicians since 1930. He was also a diplomate of the American Board of Internal Medicine.

Dr. Addis was a former Carnegie Research Scholar and Fellow, and the first Visiting Fellow at the Long Island College of Medicine, Brooklyn. He had many publications to his credit, among which were "Renal Lesion in Bright's Disease" and "Glomerular Nephritis: Diagnosis and Treatment."

## DR. WILLIAM DUNCAN REID

Dr. William Duncan Reid, F.A.C.P., of North Parsonfield, Maine, was a resident of Massachusetts for many years before his retirement. He graduated from Harvard Medical School in 1909 and during World War I served with the American Expeditionary Forces in France. During all the years of his medical life, Dr. Reid was interested in heart disease, and two books appeared under his authorship, "The Heart in Modern Practice" and "Teaching Methods in Medicine." When the first electrocardiograph machine was installed in the Boston City Hospital, Dr. Reid supervised this important department and emphasized the physiological approach to the study and understanding of heart disease. For many years, his interest in the heart during pregnancy commanded his attention and study. All of his friends profited by associating with him, and his students were admiring and loyal.

CHESTER S. KEEFER, M.D., F.A.C.P.,  
Governor for Massachusetts

## DR. BRUCE HUTCHINSON DOUGLAS

Bruce Hutchinson Douglas, A.B., M.D., F.A.C.P., Detroit, Mich., was instantly killed in an automobile accident, en route on a much needed vacation, on August 11, 1949.

Dr. Douglas was born on August 26, 1892. He graduated, A.B., 1915, from Whittier College, and M.D., 1921, from the Rush Medical School. Following graduation he served an internship and residency in the Children's Hospital and in the Herman Kiefer Hospital, Detroit. During 1924-25 he carried on postgraduate studies in preventive medicine and tuberculosis in England, Denmark and Switzerland. Following graduation and residency, Dr. Douglas devoted his life to preventive medicine and to work in the field of tuberculosis. In these fields he became an outstanding authority and teacher. For two years, 1923-25, he was a Lecturer on Tuberculosis to the undergraduate students in the University of Michigan Medical School. Later he became a Lecturer on Tuberculosis in the University of Michigan Postgraduate School of Medicine. For many years he taught preventive medicine and public health in the Wayne University College of Medicine, and in 1941 he became Professor of

## DR. W. HUARD HARGIS, JR.

Dr. W. Huard Hargis, Jr., died of poliomyelitis on August 15, 1949, in San Antonio, Texas, where he was born on December 27, 1912. Dr. Hargis was a graduate of the University of Texas School of Medicine and received the degrees of B.S. in Medicine and M.D. in 1936. He served an internship at the University of Iowa Hospital in 1936-37, and was a Fellow in Internal Medicine of the Mayo Foundation and received the degree of Master of Science in Medicine in 1942. During World War II, Dr. Hargis was a Major in the Medical Corps of the United States Army.

He was Chief of the Medical Service of the Robert B. Green Memorial Hospital, San Antonio, and Director of the Clinic of the Baptist Memorial Hospital, San Antonio. Dr. Hargis was a Diplomate of the American Board of Internal Medicine and a member of the Bexar County Medical Society, Texas State Medical Association and the American Medical Association. He has been an Associate of the American College of Physicians since 1945. In February of 1948, Dr. Hargis was elected a member of the Texas Club of Internists. He was held in high esteem by his colleagues and a most promising career was closed by his untimely death.

D. W. CARTER, JR., M.D., F.A.C.P.,  
Governor for Texas

## DR. FREDERIC A. ALLING

Dr. Frederic A. Alling died, aged 65, at his home in Montclair, N. J., on October 20, 1949. He had been ill for several months with a malignant hypertension.

He lived a life of intense activity. Always hard working and devoted to his profession, his patients and friends were devoted to him. He became one of the leading and most respected internists in the state.

He was graduated from Princeton in 1907 and from the College of Physicians and Surgeons, Columbia University, in 1911. He interned at the New York Hospital, began practice in Newark, and married Helen, daughter of Bishop Stearley. She and two sons and two daughters survive him.

In World War I Dr. Alling served overseas with the New York Hospital Unit with the rank of Captain. He was an Attending Physician at Newark City Hospital, St. Barnabas Hospital and Presbyterian Hospital, all of Newark. At St. Barnabas he had been President of the Medical Staff. He was Consulting Physician at Rahway and Newark Memorial Hospitals, the Newark Eye and Ear Infirmary, and the Essex Mountain Sanatorium. He was a former president of the Practitioners Society, and had taken an active part in the Essex County and New Jersey State Medical Societies as well as the Academy of Medicine of Northern New Jersey. He was made a Fellow of the College in 1938.

A man of great capacity and many interests, Dr. Alling will be sorely missed by patients, friends, and associates.

GEORGE H. LATHROPE, M.D., F.A.C.P.,  
Governor for New Jersey

## DR. JOHN WALTER TORBETT

Dr. J. W. Torbett, F.A.C.P., of Marlin, Texas, died on August 9, 1949, of coronary occlusion.

Dr. Torbett was born July 12, 1871, near Jacksonville, Texas. He was graduated a Bachelor of Science from Centenary College, Lampasas, Texas, in 1891, and received his medical degree from the Atlanta Medical College, Atlanta, Georgia, in 1895, graduating with highest honors. Dr. Torbett practiced continuously in Marlin, Texas, from 1896 until the time of his death. Here he established a clinic and hos-

# ANNALS OF INTERNAL MEDICINE

## AUTHOR INDEX

Volume 31, July-December, 1949

- |   |     |   |      |
|---|-----|---|------|
| ANGRIST, A., E. D. ROBBINS and —.<br>Necrosis of the renal papillae. . . . .  | 773 | Nitrogen metabolism in chronic idiopathic ulcerative colitis and its therapeutic significance. . . . .  | 282  |
| APPLEBAUM, E. and S. M. ARONSON.<br>Erythema multiforme bullosum due to sulfadiazine sensitivity controlled with procaine intravenously. <i>Case Rep.</i> . . . . .   | 146 | BOONE, B. R., G. F. ELLINGER and F. G. GILLICK. Electrocardiography of the heart and great vessels: principles and application. . . . .   | 1030 |
| ARANOW, H., JR., G. F. CAHILL and —.<br>Pheochromocytoma: diagnosis and treatment. . . . .  | 389 | BOONE, J. A. and H. G. SMITHY. Vena caval thrombosis with polycythemia and leg ulcer. <i>Case Rep.</i> . . . . .  | 513  |
| ARONSON, S. M., E. APPLEBAUM and —.<br>Erythema multiforme bullosum due to sulfadiazine sensitivity controlled with procaine intravenously. <i>Case Rep.</i> . . . . .  | 146 | BOUCOT, K. R., D. A. COOPER, E. W. MARSHALL and F. MACD. RICHARDSON. Chest x-ray surveys in general hospitals, a critical review. . . . .   | 889  |
| BARRETT, R. H. Sodium succinate—<br>an analeptic for barbiturate poisoning in man. . . . .  | 739 | BURCH, G. E. and C. T. RAY. Lower nephron syndrome. . . . .   | 750  |
| BAYNE-JONES, S. The hospital as a center of preventive medicine. . . . .  | 7   | BURCH, G. E. and T. WINSOR. A primer of electrocardiography. <i>Rev.</i> . . . .  | 171  |
| BEAKEY, J. F., E. A. GAENSLER,—and M. S. SEGAL. Pharmacodynamics of pulmonary absorption in man. I. Aerosol and intratracheal penicillin. . . . .   | 582 | CAHILL, G. F. and H. ARANOW, JR. Pheochromocytoma: diagnosis and treatment. . . . .   | 389  |
| BEAKEY, J. F., E. A. GAENSLER and M. S. SEGAL. Pharmacodynamics of pulmonary absorption in man. II. The influence of various diluents on aerosol and intratracheal penicillin. . . . .                        | 805 | CANTAROW, A. and M. TRUMPER. Clinical biochemistry. <i>Rev.</i> . . . . .   | 934  |
| BERGMAN, H. C., M. PRINZMETAL, L. L. SCHWARTZ, E. CORDAY, R. SPRITZLER, —and H. E. KRUGER. Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion. . . . . | 429 | CAPLAN, P. S., H. M. MARGOLIS and —. The use of curare (d-tubocurarine in oil and wax) in the treatment of muscle spasm in rheumatic disorders. . . . .                                     | 615  |
| BICKERMAN, L. J. and E. E. IRONS. Myocardial infarction resulting in interventricular septal perforation; report of case diagnosed during life. <i>Case Rep.</i> . . . . .                                    | 918 | CHURG, J., N. UHR and—. Hypertrophic osteoarthropathy; report of a case associated with a chordoma of the base of the skull and lymphangitic pulmonary metastases. <i>Case Rep.</i> . . . . | 681  |
| BOAS, E. P. and N. F. BOAS. Coronary artery disease. <i>Rev.</i> . . . . .  | 360 | CHUSID, J. G., J. J. McDONALD,—and J. LANGE. Correlative neuroanatomy. <i>Rev.</i> . . . . .  | 704  |
| BOCKUS, H. L., T. S. SAPPINGTON and —. Nitrogen balance studies in chronic peptic ulcer disease. . . . .  | 271 | CLARK, E., L. WALLACE and—. Electrocardiographic changes in a case of Wernicke's syndrome. <i>Case Rep.</i> . . . .   | 675  |
|   |     | COLLINS, H. S., M. FINLAND,—T. M. GÖCKE and E. B. WELLS. Present status of aureomycin therapy. . . . .  | 39   |
|   |     | COMROE, B. I. Arthritis and allied conditions. <i>Rev.</i> . . . . .  | 932  |

- GLASS, W. H. Persistent tachycardia caused by snake venom. *Case Rep.*... 517
- GOCKE, T. M., M. FINLAND, H. S. COLLINS,—and E. B. WELLS. Present status of aureomycin therapy.... 39
- GOLD, M. M. A., K. LANGE, D. WEINER and—. Studies on the mechanism of cardiac injury in experimental hypothermia..... 989
- GOLDMAN, A. M. and J. D. RIVES. A case of mesenteric venous thrombosis with survival. *Case Rep.*..... 329
- GREEN, M. A. Aerosol penicillin in allergic patients with respiratory infections..... 260
- GROB, D., W. L. GARLICK, G. G. MERRILL and H. C. FREIMUTH. Death due to parathion, an anticholinesterase insecticide. *Case Rep.*..... 899
- GRUSKIN, B. J. Aureomycin in acute infectious mononucleosis. *Case Rep.* 678
- GUTTENTAG, O. E. On the clinical entity..... 484
- HAMILTON, K. A. Pulmonary disease manifestations of ankylosing spondylarthritis..... 216
- HARRIS, N. G., Editor. Modern trends in psychological medicine. *Rev.*.... 171
- HARTZ, A. S. The diagnosis of pneumonia preceding tuberculosis..... 1066
- HARVEY, W. P., S. A. LEVINE and—. Clinical auscultation of the heart. *Rev.*..... 704
- HAYES, E. W., Editor. The fundamentals of pulmonary tuberculosis and its complications, for the student, the teacher, and the practicing physician. *Rev.*..... 532
- HERSH, A. H., R. M. STECHER,—and W. M. SOLOMON. The heredity of gout and its relationship to familial hyperuricemia..... 595
- HILKER, A. W. The shoulder-hand syndrome: a complication of coronary artery disease..... 303
- IRONS, E. E., L. J. BICKERMAN and—. Myocardial infarction resulting in interventricular septal perforation: report of a case diagnosed during life. *Case Rep.*..... 918
- JONES, C. C., P. H. MORTON and—. Tropical eosinophilia with report of a case treated with penicillin. *Case Rep.*..... 1112
- KANNER, L. Child psychiatry. *Rev.*... 362
- KARPMAN, B. Case studies in the psychopathology of crime. *Rev.*.... 170
- KEMPNER, W. Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet..... 821
- KLEINER, I. S. Human biochemistry. *Rev.*..... 1134
- KONORSKI, J. Conditioned reflexes and neuron organization. *Rev.*.... 1133
- KRONENBERG, S., C. S. DWYER,—and M. SAKLAD. Anginal syndrome during sodium succinate therapy. *Case Rep.*..... 148
- KRUGER, H. E., M. PRINZMETAL, L. L. SCHWARTZ, E. CORDAY, R. SPRITZLER, H. C. BERGMAN and—. Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion..... 429
- KURZ, E. R. H., E. L. CREHAN and C. THOMSON. Salmonella endocarditis with streptomycin failure. *Case Rep.* 497
- LANGE, J., J. J. McDONALD, J. C. CHUSID and—. Correlative neuroanatomy. *Rev.*..... 704
- LANGE, K., D. WEINER and M. M. A. GOLD. Studies on the mechanism of cardiac injury in experimental hypothermia..... 989
- LEVINE, S. A. and W. P. HARVEY. Clinical auscultation of the heart. *Rev.*..... 704
- LICHTMAN, S. S. Diseases of the liver, gallbladder, and bile ducts. *Rev.*.... 531
- LINTON, R. R. The surgical treatment of bleeding esophageal varices by portal systemic venous shunts with a report of 34 cases..... 794
- LONGCOPE, W. T. and J. A. LUETSCHER, JR. The use of BAL (British Anti-Lewisite) in the treatment of the injurious effects of arsenic, mercury and other metallic poisons..... 545
- LOWEN, H. J. and H. E. B. PARDEE. Unipolar extremity leads in records with large Q<sub>3</sub>..... 456

- PRINZMETAL, M., E. CORDAY, R. SPRITZLER and—. Studies on the coronary circulation. VII. The remarkable reserve power of the heart. . . . 450
- RAISBECK, M. J., S. A. THOMPSON and —. The surgical rehabilitation of the coronary cripple. . . . . 1010
- RAY, C. T., G. E. BURCH and—. Lower nephron syndrome. . . . . 750
- REES, J. R., Editor. Modern practice in psychological medicine. *Rev.* . . . . 1133
- RENNER, W. F. Pulmonary embolism with acute cor pulmonale and extremely rapid ventricular rate in a young, active, apparently healthy adult. *Case Rep.* . . . . . 1090
- RICE, M. L., JR., C. E. THOMPSON and —. Secondary amyloidosis in spinal cord injury. . . . . 1057
- RICHARDSON, F. MACD., K. R. BOUCOT, D. A. COOPER, E. W. MARSHALL and —. Chest x-ray surveys in general hospitals, a critical review. . . . . 889
- RIVES, J. D., A. M. GOLDMAN and—. A case of mesenteric venous thrombosis with survival. *Case Rep.* . . . . 329
- ROBBINS, E. D. and A. ANGRIST. Necrosis of renal papillae. . . . . 773
- ROESLER, H., W. DRESSLER and —. An atlas of electrocardiography. *Rev.* . . . . . 933
- ROSE, H. M. The clinical manifestations and laboratory diagnosis of rickettsialpox. . . . . 871
- ROSENBLATT, P., S. D. SPATT and—. The incidence of hypertension in portal cirrhosis: a study of 80 necropsied cases of portal cirrhosis. . . . . 479
- ROSENBLOOM, S. E. Superior vena cava obstruction in primary cancer of the lung. . . . . 470
- ROSENBLUM, A. H. Typhoid and paratyphoid fever in immunized subjects. . . . . 235
- ROSENTHAL, N., J. M. SPITZER, —M. WEINER and S. SHAPIRO. Pulmonary embolism: its incidence at necropsy in relation to peripheral thrombosis. . . . . 884
- SAKLAD, M., C. S. DWYER, S. KRONENBERG and—. Anginal syndrome during sodium succinate therapy. *Case Rep.* . . . . . 148
- SAPPINGTON, T. S. and H. L. BOCKUS. Nitrogen balance studies in chronic peptic ulcer disease. . . . . 271
- Nitrogen metabolism in chronic idiopathic ulcerative colitis and its therapeutic significance. . . . . 282
- SCHINDLER, R., M. M. MOURAO and—. Pancreatic lithiasis and gastritis (cases with gastroscopic observations). . . . . 83
- SCHWAB, L., G. L. SMILEY and W. P. MEYN. Xiphosternal crunch: an analysis of 106 cases among 3,224 army separatees. . . . . 228
- SCHWARTZ, L. L., M. PRINZMETAL, —E. CORDAY, R. SPRITZLER, H. C. BERGMAN and H. E. KRUGER. Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion. . . . . 429
- SEABURY, J. H. Stilbamidine in the treatment of histoplasmosis. *Case Rep.* . . . . . 520
- SEGAL, M. S., E. A. GAENSLER, J. F. BEAKEY and—. Pharmacodynamics of pulmonary absorption in man. I. Aerosol and intratracheal penicillin. . . . . 582
- SEGAL, M. S., J. F. BEAKEY, E. A. GAENSLER and—. Pharmacodynamics of pulmonary absorption in man. II. The influence of various diluents on aerosol and intratracheal penicillin. . . . . 805
- SHAPIRO, S., J. M. SPITZER, N. ROSENTHAL, M. WEINER and—. Pulmonary embolism: its incidence at necropsy in relation to peripheral thrombosis. . . . . 884
- SIEGEL, M. B. and A. J. FRIEDMAN. Fatal mercurialism due to prolonged intravenous administration of a mercurial diuretic. *Case Rep.* . . . . . 343
- SIGLER, L. Cardiovascular disease. *Rev.* . . . . . 934
- SMILEY, G. L., L. SCHWAB, —and W. P. MEYN. Xiphosternal crunch: an analysis of 106 cases among 3,224 army separatees. . . . . 228
- SMITH, D. T. Immunologic types of blastomycosis: a report on 40 cases. . . . . 463
- SMITH, J. G. The electrocardiographic syndrome following paroxysmal tachycardia. *Case Rep.* . . . . . 504

- WELLS, E. B., M. FINLAND, H. S. COLLINS, T. M. GOCKE and—. Present status of aureomycin therapy 39
- WHIPPLE, A. O. An evaluation of radical surgery for carcinoma of the pancreas and ampullary region..... 624
- WHITE, P. D. and C. FERRERO. Research problems in coronary heart disease..... 33
- WHITE, P. D., F. E. GARDNER and—. Coronary occlusion and myocardial infarction associated with chronic rheumatic heart disease..... 1003
- WHITE, P. D., J. H. CURRENS and—. Great reduction in heart size attending the clearing of congestive heart failure in a man with hypertensive and coronary heart disease. *Case Rep.*..... 912
- WINSOR, T., G. E. BURCH and—. A primer of electrocardiography. *Rev.* 171
- WOLF, S. Summary of evidence relating life situation and emotional response to peptic ulcer..... 637
- WONG, Y. T., H. PACKER and—. Penicillin and penicillin-malaria in the treatment of tabes dorsalis..... 96
- WOODWARD, T. E. Chloromycetin and aureomycin: therapeutic results.. 53
- YATER, W. M. Fundamentals of internal medicine. *Rev.*..... 359
- ZHEUTLIN, B. Endocarditis caused by organism morphologically identified as *C. diphtheriae*. *Case Rep.*..... 339
- ZIMMERMAN, I. and N. MANN. Boeck's sarcoid: a case of sarcoidosis complicated by pulmonary emphysema and cor pulmonale. *Case Rep.*..... 153



- Cardiology. W. EVANS. *Rev.*..... 172
- Cardiovascular disease. L. H. SIGLER.  
*Rev.*..... 934
- Cardiovascular diseases, A physiologic  
and clinical study of —. Heart:—.  
A. A. LUISADA. *Rev.*..... 1133
- Case studies in the psychopathology  
of crime. B. KARPMAN. *Rev.*..... 170
- C. diphtheriae*, Endocarditis caused by  
organism morphologically and cultur-  
ally identified as—. B. ZHEUTLIN.  
*Case Rep.*..... 339
- Chest x-ray surveys in general hospitals,  
a critical review. K. R. BOUCOT,  
D. A. COOPER, E. W. MARSHALL and  
F. MACD. RICHARDSON..... 889
- Child psychiatry. L. KANNER. *Rev.*... 362
- Chloromycetin and aureomycin: thera-  
peutic results. T. E. WOODWARD.... 53
- Chordoma of the base of the skull, Re-  
port of a case associated with a—and  
lymphangitic pulmonary metastases.  
Hypertrophic osteoarthropathy;—.  
N. UHR and J. CHURG. *Case Rep.*... 681
- Circulation, Studies on the coronary—.  
VI. Loss of myocardial contractility  
after coronary artery occlusion. M.  
PRINZMETAL, L. E. SCHWARTZ, E.  
CORDAY, R. SPRITZLER, H. C. BERG-  
MAN and H. E. KRUGER..... 429
- VII. The remarkable reserve power  
of the heart. E. CORDAY, R. SPRITZ-  
LER and M. PRINZMETAL..... 450
- Cirrhosis, The incidence of hypertension  
in portal—: a study of 80 necropsied  
cases of portal cirrhosis. S. D.  
SPATT and P. ROSENBLATT..... 479
- Clinical allergy. L. TUFT. *Rev.*..... 703
- Clinical biochemistry. A. CANTAROW  
and M. TRUMPER. *Rev.*..... 934
- Clinical entity, On the—. O. E.  
GUTTENTAG..... 484
- Clinical manifestations and laboratory  
diagnosis of rickettsialpox, The—.  
H. M. ROSE..... 871
- Clinical observations on atypical lichen  
planus and related dermatoses pre-  
sumably due to atabrine toxicity. A.  
FEDER..... 1078
- Colitis, Nitrogen metabolism in chronic  
idiopathic ulcerative—and its thera-  
peutic significance. T. S. SAPPING-  
TON and H. L. BOCKUS..... 282
- Conditioned reflexes and neuron organ-  
ization. J. KONORSKI. *Rev.*..... 1133
- Coronary artery disease, A complica-  
tion of—. The shoulder-hand syn-  
drome:—. A. W. HILKER..... 303
- Coronary artery disease. E. P. BOAS  
and N. F. BOAS. *Rev.*..... 360
- Coronary circulation, Studies on the—.  
VI. Loss of myocardial contractility  
after coronary artery occlusion. M.  
PRINZMETAL, L. E. SCHWARTZ, E.  
CORDAY, R. SPRITZLER, H. C. BERG-  
MAN and H. E. KRUGER..... 429
- VII. The remarkable reserve power  
of the heart. E. CORDAY, R. SPRITZ-  
LER and M. PRINZMETAL..... 450
- Coronary cripple, The surgical rehabili-  
tation of the—. S. A. THOMPSON  
and M. J. RAISBECK..... 1010
- Coronary heart disease, Research prob-  
lems in—. P. D. WHITE and C.  
FERRERO..... 33
- Coronary occlusion and myocardial  
infarction associated with chronic  
rheumatic heart disease. F. E.  
GARDNER and P. D. WHITE..... 1003
- Crime, Case studies in the psychopath-  
ology of—. B. KARPMAN. *Rev.*.... 170
- Curare (d-tubocurarine in oil and wax),  
The Use of—in the treatment of  
muscle spasm in rheumatic disorders.  
H. M. MARGOLIS and P. S. CAPLAN... 615
- Cysts, splenic—, Diagnostic features of  
—with case report and review of the  
literature. A. A. FISCHL and J.  
PAPPS. *Case Rep.*..... 1105
- Cytology, exfoliative—in cancer diag-  
nosis, A survey of the actualities and  
potentialities of—. G. N. PAPANI-  
COLAOU..... 661
- D**EATH due to parathion, an anti-  
cholinesterase insecticide. D.  
GROB, W. L. GARLICK, G. G. MER-  
RILL and H. C. FREIMUTH. *Case  
Rep.*..... 899
- Dermatoses, Clinical observations on  
atypical lichen planus and related—  
presumably due to atabrine toxicity.  
A. FEDER..... 1078
- Diagnosis of pneumonia preceding tu-  
berculosis, The—. A. S. HARTZ..... 1066

- Gastric mucosa, Prolapsed—: a possible cause of "gastric" symptoms in right heart failure. M. MELAMED and A. MELAMED..... 245
- Gastritis, Pancreatic lithiasis and— (cases with gastroscopic observations). M. M. MOURAO and R. SCHINDLER..... 83
- Gout, The heredity of—and its relationship to familial hyperuricemia. R. M. STECHER, A. H. HERSH and W. M. SOLOMON..... 595
- Gouty arthritis and its complications, The diversity of—. J. H. TALBOTT.. 555
- Graves' disease, Hepatosplenomegaly and liver damage in—. R. S. WALLERSTEIN and W. J. WALKER. *Case Rep.*..... 904
- H** EART and great vessels, Electrokymography of the—: principles and application. B. R. BOONE, G. F. ELLINGER and F. G. GILICK..... 1030
- Heart and kidney disease, Treatment of—and of hypertensive and arteriosclerotic vascular disease with the rice diet. W. KEMPNER..... 821
- Heart: A physiologic and clinical study of cardiovascular diseases. A. A. LUISADA. *Rev.*..... 1133
- Heart, Clinical auscultation of the—. S. A. LEVINE and W. P. HARVEY. *Rev.*..... 704
- Heart disease, chronic rheumatic—, Coronary occlusion and myocardial infarction associated with—. F. E. GARDNER and P. D. WHITE..... 1003
- Heart disease, Research problems in coronary—. P. D. WHITE and C. FERRERO..... 33
- Heart failure, A possible cause of "gastric" symptoms in right—. Prolapsed gastric mucosa:—. M. MELAMED and A. MELAMED..... 245
- Heart failure, congestive, in a man with hypertensive and coronary heart disease, Great reduction in heart size attending the clearing of—. J. H. CURRENS and P. D. WHITE. *Case Rep.*..... 912
- Heart failure, New light on the pharmacodynamics of—. *Edit.*..... 524
- Hemophilus influenzae* endocarditis lenta, Streptomycin therapy of—. W. S. MIDDLETON. *Case Rep.*..... 511
- Hemorrhage, Subacute bacterial endocarditis presenting as a subarachnoid—(report of a case with recovery). R. A. STARRS. *Case Rep.*..... 139
- Hemorrhagic diatheses, The etiology and management of the—. C. A. DOAN..... 967
- Hepatic insufficiency, The prognosis and treatment of—. C. J. WATSON. 405
- Hepatitis, Viral—: problems and progress. J. R. NEEFE..... 857
- Hepatosplenomegaly and liver damage in Graves' disease. R. S. WALLERSTEIN and W. J. WALKER. *Case Rep.* 904
- Heredity of gout and its relationship to familial hyperuricemia, The—. R. M. STECHER, A. H. HERSH and W. M. SOLOMON..... 595
- Histoplasmosis, Stilbamidine in the treatment of—. J. H. SEABURY. *Case Rep.*..... 520
- Hormones, The—: physiology, chemistry and applications. G. PINCUS and K. V. THIMANN, Editors. *Rev.*... 169
- Hospital, The—as a center of preventive medicine. S. BAYNE-JONES..... 7
- Human biochemistry. I. S. KLEINER. *Rev.*..... 1134
- Hypersensitivity to folic acid. D. C. MITCHELL, R. W. VILTER and C. F. VILTER. *Case Rep.*..... 1102
- Hypertension in portal cirrhosis, The incidence of—: a study of 80 necropsied cases of portal cirrhosis. S. D. SPATT and P. ROSENBLATT..... 479
- Hypertension, Recent advances in the pathogenesis and treatment of essential—. G. E. WAKERLIN..... 312
- Hypertensive and arteriosclerotic vascular disease, Treatment of heart and kidney disease and of—with the rice diet. W. KEMPNER..... 821
- Hyperuricemia, The heredity of gout and its relationship to familial—. R. M. STECHER, A. H. HERSH and W. M. SOLOMON..... 595
- Hypothermia, Studies on the mechanism of cardiac injury in experimental—. K. LANGE, D. WEINER and M. M. A. GOLD..... 989

- George, Shaul. . . . . 185  
 Gichner, Joseph Enoch. . . . . 372  
 Graves, William Washington. . . . . 962  
 Hall, Frederic W. . . . . 372  
 Hargis, W. Huard, Jr. . . . . 1157  
 Jack, Cecil McKee. . . . . 964  
 Lewis, Thomas Krapfel. . . . . 963  
 Litvak, Abraham M. . . . . 186  
 Lockard, G. Carroll. . . . . 964  
 Louria, Alexander L. . . . . 543  
 Meehan, John William. . . . . 544  
 Miller, Sydney R. . . . . 183  
 Morgan, William Gerry. . . . . 539  
 Muniz, Jorge Rodriguez. . . . . 714  
 Pemberton, Ralph. . . . . 543  
 Redwood, Frank Harrell. . . . . 714  
 Reid, William Duncan. . . . . 1155  
 Rudisill, Hillyer, Jr. . . . . 1156  
 Rutledge, Clifford P. . . . . 372  
 Simonds, Paul Edward. . . . . 965  
 Skinner, George Alfred. . . . . 544  
 Soley, Mayo Hamilton. . . . . 541  
 Thomas, Anne Heath. . . . . 186  
 Torbett, John Walter. . . . . 1157  
 West, Randolph. . . . . 184  
 Westmoreland, Robert Edward, Sr. . . . . 965  
 Westra, Jacob John. . . . . 966  
 Obstetric analgesia and anesthesia.  
 F. F. SNYDER. *Rev.* . . . . . 705  
 Organic disease, Emotional factors in—  
 W. C. MENNINGER. . . . . 207  
 Osteoarthropathy, hypertrophic—; re-  
 port of a case associated with a chor-  
 doma of the base of the skull and  
 lymphangitic pulmonary metastases.  
 N. UHR and J. CHURG. *Case Rep.* . . . . 681  
 PANCREATIC lithiasis and gastritis  
 (cases with gastroscopic observa-  
 tions). M. M. MOURAO and R.  
 SCHINDLER. . . . . 83  
 Pancreatitis, Calcareous—. C. A.  
 DOMZALSKI, JR. . . . . 650  
 Paraplegia secondary to metastatic  
 carcinoma treated with stilbestrol.  
 I. S. EDELMAN. *Case Rep.* . . . . . 1098  
 Parathion, Death due to—, an anti-  
 cholinesterase insecticide. D. GROB,  
 W. L. GARLICK, G. G. MERRILL and  
 H. C. FREIMUTH. *Case Rep.* . . . . . 899  
 Paratyphoid, Typhoid and—fever in  
 immunized subjects. A. H. ROSEN-  
 BLUM. . . . . 235  
 Penicillin, Aerosol and intratracheal—.  
 Pharmacodynamics of pulmonary  
 absorption in man. I.—. E. A.  
 GAENSLER, J. F. BEAKEY and M. S.  
 SEGAL. . . . . 582  
 II. The influence of various diluents  
 on aerosol and intratracheal peni-  
 cillin. J. F. BEAKEY, E. A. GAEN-  
 SLER and M. S. SEGAL. . . . . 805  
 Penicillin, Aerosol—in allergic patients  
 with respiratory infections. M. A.  
 GREEN. . . . . 260  
 Penicillin and penicillin-malaria in the  
 treatment of tabes dorsalis. H.  
 PACKER and Y. T. WONG. . . . . 96  
 Penicillin, Putrid empyema with a  
 bronchopleural fistula successfully  
 treated with—. A. L. FORSGREN.  
*Case Rep.* . . . . . 691  
 Penicillin, Tropical eosinophilia with  
 report of a case treated with—. P.  
 H. MORTON and C. C. JONES. *Case  
 Rep.* . . . . . 1112  
 Peptic ulcer disease, Nitrogen balance  
 studies in chronic—. T. S. SAPPING-  
 TON and H. L. BOCKUS. . . . . 271  
 Peptic ulcer, Summary of evidence re-  
 lating life situation and emotional  
 response to—. S. WOLF. . . . . 637  
 Pharmacodynamics of heart failure,  
 New light on the—. *Edit.* . . . . 524  
 Pharmacodynamics of pulmonary ab-  
 sorption in man. I. Aerosol and  
 intratracheal penicillin. E. A. GAEN-  
 SLER, J. F. BEAKEY and M. S. SEGAL. . . . 582  
 II. The influence of various diluents  
 on aerosol and intratracheal peni-  
 cillin. J. F. BEAKEY, E. A. GAEN-  
 SLER and M. S. SEGAL. . . . . 805  
 Pheochromocytoma: diagnosis and  
 treatment. G. F. CAHILL and H.  
 ARANOW, JR. . . . . 389  
 Phlebitis and the diagnosis of throm-  
 boangiitis obliterans. E. A. ED-  
 WARDS. . . . . 1019  
 Pituitary-adrenal relationships, Some  
 aspects of adrenal cortical function  
 and—. *Edit.* . . . . 925  
 Pneumonia, The diagnosis of—preced-  
 ing tuberculosis. A. S. HARTZ. . . . . 1066  
 Poisoning, barbiturate—in man,  
 Sodium succinate—an analeptic for  
 —. R. H. BARRETT. . . . . 739

- S**ALMONELLA endocarditis with streptomycin failure. E. R. H. KURZ, E. L. CREHAN and C. THOMSON. *Case Rep.*..... 497
- Sarcoid, Boeck's—: a case of sarcoidosis complicated by pulmonary emphysema and cor pulmonale. I. ZIMMERMAN and N. MANN. *Case Rep.*..... 153
- Sarcoma, Kaposi's—with secondary involvement of the jejunum, perforation and peritonitis. N. MITCHELL and I. A. FEDER. *Case Rep.*.... 324
- Shoulder-hand syndrome, The—: a complication of coronary artery disease. A. W. HILKER..... 303
- Sodium succinate—an analeptic for barbiturate poisoning in man. R. H. BARRETT..... 739
- Sodium succinate therapy, Anginal syndrome during—. C. S. DWYER, S. KRONENBERG and M. SAKLAD. *Case Rep.*..... 148
- Sound. Xiphosternal crunch: an analysis of 106 cases among 3,224 army separates. I. SCHWAB, G. L. SMILEY and W. P. MEYN..... 228
- Spinal cord injury, Secondary amyloidosis in—. C. E. THOMPSON and M. L. RICE, JR..... 1057
- Splenic cysts, Diagnostic features of—with case report and review of the literature. A. A. FISCHL and J. PAPPS. *Case Rep.*..... 1105
- Spondylarthritis, Pulmonary disease manifestations of ankylosing—. K. A. HAMILTON..... 216
- Stilbamidine in the treatment of histoplasmosis. J. H. SEABURY. *Case Rep.*..... 520
- Stilbestrol, Paraplegia secondary to metastatic carcinoma treated with—. I. S. EDELMAN. *Case Rep.*..... 1098
- Streptomycin failure, Salmonella endocarditis with—. E. R. H. KURZ, E. L. CREHAN and C. THOMSON. *Case Rep.*..... 497
- Streptomycin therapy of *Hemophilus influenzae* endocarditis lenta. W. S. MIDDLETON. *Case Rep.*..... 511
- Studies on the mechanism of cardiac injury in experimental hypothermia. K. LANGE, D. WEINER and M. M. A. GOLD..... 989
- Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion. M. PRINZMETAL, L. E. SCHWARTZ, E. CORDAY, R. SPRITZLER, H. C. BERGMAN and H. E. KRUGER..... 429
- VII. The remarkable reserve power of the heart. E. CORDAY, R. SPRITZLER and M. PRINZMETAL..... 450
- Sulfadiazine sensitivity, Erythema multiforme bullosum due to—controlled with procaine intravenously. E. APPELBAUM and S. M. ARONSON. *Case Rep.*..... 146
- Summary of evidence relating life situation and emotional response to peptic ulcer. S. WOLF..... 637
- Surgery, radical—for carcinoma of the pancreas and ampullary region, An evaluation of—. A. O. WHIPPLE.... 624
- Surgical rehabilitation of the coronary cripple, The—. S. A. THOMPSON and M. J. RAISBECK..... 1010
- Surgical treatment of bleeding esophageal varices by portal systemic venous shunts with a report of 34 cases, The—. R. R. LINTON..... 794
- Survey of the actualities and potentialities of exfoliative cytology in cancer diagnosis, A—. G. N. PAPANICOLAOU..... 661
- Syphilis: its course and management. E. W. THOMAS. *Rev.*..... 361
- T**ABES dorsalis, Penicillin and penicillin-malaria in the treatment of—. H. PACKER and Y. T. WONG.... 96
- Tachycardia, Persistent—caused by snake venom. W. H. GLASS. *Case Rep.*..... 517
- Tachycardia, The electrocardiographic syndrome following paroxysmal—. J. G. SMITH. *Case Rep.*..... 504
- Thromboangiitis obliterans, Phlebitis and the diagnosis of—. E. A. EDWARDS..... 1019
- Thrombosis, A case of mesenteric venous—with survival. A. M. GOLDMAN and J. D. RIVES. *Case Rep.*..... 329
- Thrombosis. Pulmonary embolism: its incidence at necropsy in relation to



pharmacologic and mechanical aspects of direct medication of the lung in man. Penicillin was chosen for this study for several reasons. It is, at present, the most frequently used agent in this form of therapy. It is free from serious toxic side reactions; it is not inactivated in the presence of pus; it is fairly stable in body fluids at freezing temperatures, and its assay in these fluids, although cumbersome, is readily accomplished by a trained bacteriologist.

The various factors requiring study are: (1) the pharmacodynamics of absorption and excretion following intratracheal and aerosol administration as contrasted to parenteral administration; (2) the action, if any, of various vehicles, other than saline, on absorption; (3) the effect of suppuration of the lung on the absorption mechanism; and lastly, (4) the relative efficiency of various methods of aerosolizing therapeutic agents. This report deals with the pharmacodynamics of absorption and excretion from the normal human lung.

Absorption from normal alveoli involves a more complex mechanism than absorption from muscle or subcutaneous tissue. Fluids must pass through the epithelium-lined wall of the alveoli and then cross the endothelium-lined capillaries into the blood stream. An alternative route is presented by the endothelium-lined lymphatics with which the alveoli are richly supplied. It is well known that fluids are absorbed from the bronchioles, bronchi and even the trachea. The relatively small surface area of the tracheobronchial tree as compared to that of the alveoli, makes absorption from the tracheobronchial mucosa quantitatively unimportant. As previously mentioned, the literature contains few references to the manner in which molecules of various sizes are absorbed from the lungs. The only studies recorded have been made in relation to war gas poisoning, pulmonary edema, and in Drinker's fundamental work on the lymphatic drainage of the lungs. Winternitz and Smith,<sup>6</sup> after the First World War, demonstrated that physiologic saline was rapidly absorbed when injected into the trachea of anesthetized dogs. Phenolsulfonphthalein, similarly administered, appeared almost immediately in the urine. Courtice and Phipps,<sup>7</sup> more recently in the course of studies with phosgene poisoning, administered water, physiologic saline and serum endotracheally to anesthetized rabbits and dogs and collected the flow from the right lymphatic duct in the latter. They were able to calculate the amount of fluid absorbed from the lungs by comparing the normal heart/lung weight ratio to that found after sacrificing the experimental animals at various intervals. Figure 1, taken from their article, illustrates their findings: 80 per cent of the water and 23 per cent of the saline were absorbed within the first hour. Serum absorbed very slowly, about four days being required for complete removal of all the material. The lymph flow was not appreciably increased above the normal; thus very little of this fluid was absorbed by the lymphatics. The ease with which water and molecules the size of sodium chloride and even phenolsulfonphthalein are absorbed from the lung is now evident. Drinker<sup>8</sup> in similarly arranged experiments,

demonstrated the ease of absorption of a 1 per cent aqueous solution of Evans Blue (T-1824, a dye with a fairly large molecular weight). Direct blood capillary absorption from the alveoli was demonstrated since the plasma became blue even when both the right lymphatic and thoracic ducts were cannulated. The lung lymphatics were shown to offer a further route of absorption, inasmuch as the right duct lymph became deeply blue. When the dye was vaporized in watery solution and the blue mist inhaled by the animal, the plasma soon became blue. Cannulation of the right lymphatic duct again showed dye absorption, but this quantity was considered insignificant as compared to that absorbed directly into the blood. T-1824 was

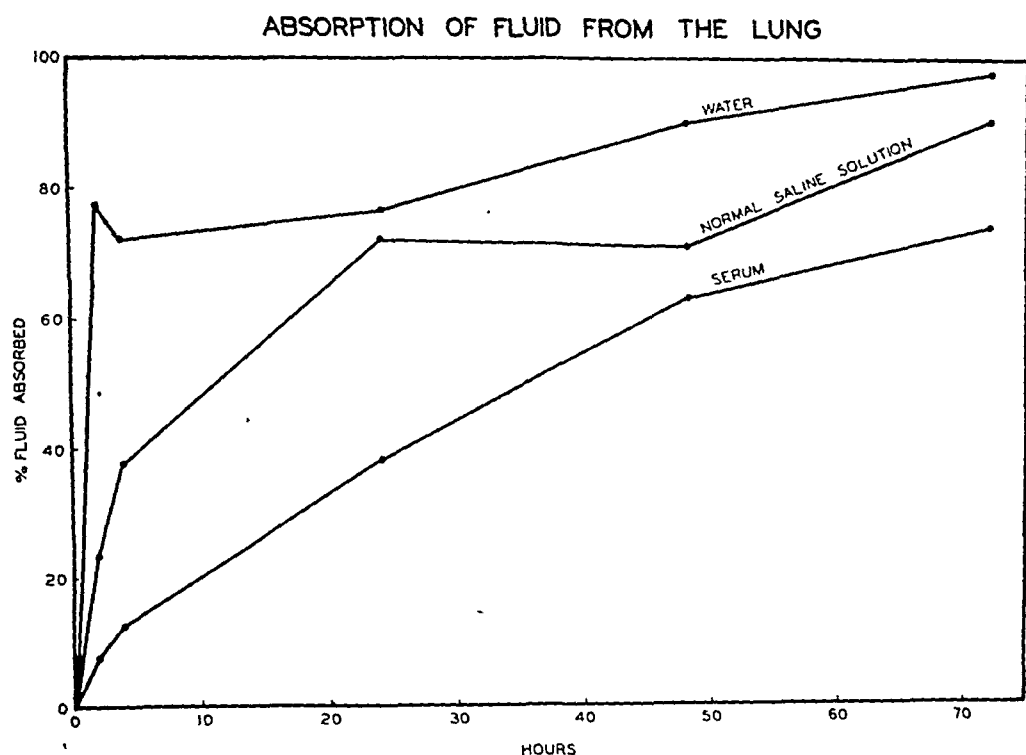


FIG. 1. Absorption of fluid from the lung. (After Courtice and Phipps, 1946. Courtesy of the Journal of Physiology.)

then instilled into the trachea in a 1 per cent solution dissolved in dog plasma and no dye appeared in either the blood or the lymphatics during the course of four hours. Since the dye has been shown to combine with the albumin molecule,<sup>9</sup> this further confirmed the slow absorption of serum from the lung. Apparently the alveolar wall presents an effective barrier to molecules over a certain size. Purified bovine serum albumin, crystallized egg albumin and hemoglobin were shown by Drinker to enter the lymphatics in traces only and, to an even lesser extent, the blood capillaries. He suggested that the molecule of penicillin, which is much smaller than that of egg albumin, might freely enter the blood stream from the alveoli.

A rational approach to the study of absorption and excretion of penicillin administered by the aerosol route necessitates an accurate determination of the amount of the active agent which actually reaches the pulmonary epithelium. It would seem, at first, that this amount might be calculated by comparing the total urinary excretion of the intramuscularly administered penicillin to that excreted following aerosol administration. If no penicillin were inactivated or detoxified within the body, such a comparison would hold. However, it is well established that only 40 to 60 per cent of parenterally administered penicillin can be recovered from the urine.<sup>10, 11, 12</sup> Moreover, the processes by which the balance of the biotherapeutic agent is detoxified or inactivated and the organs involved in this mechanism have not been established. Penicillin given intravenously to patients with complete renal shutdown disappears from the blood at a logarithmic rate with a half-life of about two hours.<sup>13</sup> Any interference with urinary excretion, due to renal insufficiency or drugs competing with penicillin for tubular excretion, such as diodrast, p-aminohippuric acid, caronamide, and others, may reduce the percentage of excreted penicillin in the urine to 30 per cent or less.<sup>12, 14, 15, 16</sup> Thus it appears that the amount of penicillin excreted is inversely related to the time of exposure within the body as a whole.

It also seems apparent that the capacity of the specific organ (the site of administration) to inactivate penicillin will inversely affect the urinary excretion. The influence of muscle or gastrointestinal mucosa on penicillin has been well established, but the effect which the pulmonary epithelium exerts is not known. It would, therefore, appear desirable to administer the drug into the tracheobronchial tree in such a fashion that no losses occur. If the percentage of urinary excretion under such conditions were known, a comparison with the excretion of aerosolized penicillin would be valid, and the effectiveness of this latter mode of administration could be calculated. Large losses with inhalational administration may be expected, largely due to technical difficulties. Loss in the apparatus and in the mouth can be relatively easily determined, as described elsewhere.<sup>17</sup> However, it is not so easy to determine the amount of active agent lost to the outside air. This loss may be expected to be the largest due to the following: (1) part of the inspired air (the dead space air) does not reach the alveoli and, therefore, most of the fluid particles are not removed; (2) the smallest droplets may enter the alveoli and leave them again on expiration without having been deposited; and (3) prevention of some loss to the outside air during aerosolization is impossible. A quantitative basis for the study of absorption and excretion following pulmonary administration requires a method by which the above mentioned losses are eliminated. We therefore elected to administer penicillin solution directly into the tracheobronchial tree by endotracheal catheter.

#### METHODS

The procedure used for endotracheal catheterization was identical to that used by the Thoracic Surgical Service to instill radio-opaque oil for



bronchography. Nembutal 0.1 gm., was given on the eve of, and again two hours before the procedure, to reduce the incidence of reactions to the topical anesthetic.<sup>18</sup> Breakfast was withheld and 60 mg. of codeine were given prior to intubation. A syringe with 0.3 gm. of Sodium Luminal in solution was on hand at all times to combat reactions (none occurred). The oropharynx was sprayed lightly with a 2 per cent Pontocaine solution (tetracaine) and a No. 12 French urethral catheter was passed through the nostril into the trachea during deep inspiration. Pontocaine, 4 c.c. of a 0.25 per cent solution, was instilled immediately and again five minutes later, after the catheter had been withdrawn sufficiently to assure the position of its tip above the carina. No more than a total of 2 c.c. of the 2 per cent solution (0.04 gm.) was used at any time. Cough was then encouraged to insure even distribution of the anesthetic solution throughout the tracheobronchial tree. Within a few minutes, the cough reflex was completely abolished. One hundred thousand units of Crystalline Penicillin G Potassium in 10 c.c. of saline were then injected through the catheter while the patient assumed various positions designed to effect an even flow of the penicillin solution throughout his lungs.

Nine patients were treated in this fashion. Blood was withdrawn at one half-hour, one hour and every hour thereafter for six hours and occasionally up to 10 hours. Urines were collected at one, two, four, eight and 24 hours and assayed separately.

To compare the results of parenterally administered penicillin, 10 volunteers were given 100,000 units intramuscularly and bloods and urines were assayed similarly. This was done to avoid errors of comparison which might arise from variations in both our technic of penicillin assay and the type of penicillin used and those of other workers.

For the aerosol studies, the Vaponefrin nebulizer with an attached, humidified, rebreathing bag was used. Of various apparatus combinations tested, this gave the most consistently high blood levels.<sup>17</sup> Apparatus and mouth rinses were assayed to estimate measurable wastage.

Using Rammelkamp's strain of highly penicillin sensitive beta hemolytic streptococci (No. 98), we determined the penicillin levels by his serial dilution method.<sup>19</sup> The only modification was the use of Group O human red blood cells as an indicator instead of horse or sheep cells, in order to avoid hemolysis.<sup>20</sup> The smallest amount of penicillin definitely detectable by this method was 0.019 unit per c.c. of serum. In the lowest dilutions, the problem of the inactivation of penicillin by serum arises.<sup>21</sup> In the first tube, the serum concentration by this method was 28 per cent. According to Eagle's chart,<sup>22</sup> a multiplication factor of 1.5 was necessary to obtain the correct value for the penicillin G content of this first indicator tube. Since most of the literature on penicillin sensitivity was written before this was generally understood, we have omitted this correction factor intentionally. In all the other dilutions except the first, this factor becomes unimportant since broth was used throughout for dilutions. Bloods and urines were

refrigerated for no longer than 24 hours. Storage for longer periods of time caused a loss in penicillin activity detectable by this method. Urines were not buffered since it has been shown that penicillin excreted in the urine is more stable than commercial penicillin and will tolerate a pH as low as 2.2 for long periods of time.<sup>23</sup> This method of assay is no more accurate than other methods of biological assay involving serial dilution. Each numerically expressed level signified that the specimen contains about half as much active substance as would be needed for a positive reaction in the next tube. In order not to give a false impression of accuracy, we have used the values of 0.16, 0.08, 0.04, 0.02, etc., rather than the values obtained by serially dividing 20 (the number of units per c.c. of standard) by 2, namely 10 . . . 2.5 . . . 0.625 . . . 0.156, 0.078, 0.039, 0.019.

### RESULTS

A total of 297 specimens were assayed, of which 167 were bloods, 108 urines and 22 apparatus and mouth rinses. Ten volunteers received 100,000 units of penicillin intramuscularly in 1 c.c. of saline (chart 1). The results

CHART I

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline (K-Salt) Penicillin (C.S.C.) in 1 c.c. Saline by the Intramuscular Route in 10 Subjects

	Blood							Urinary Excretion				
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.
No. 1	1.25	.63	.08	—	.02	—	—	24,960	5,070	—	390	27
No. 2	.16	.16	.08	—	—	—	—	—	—	—	—	—
No. 3	.31	.63	.31	.08	.04	.02	.00	4,368	10,250	13,750	2,340	300
No. 4	.63	.31	.08	.04	.00	.00	.00	72,500	10,750	4,750	796	900
No. 5	1.25	.63	.31	.08	.04	.00	.00	18,750	4,750	12,250	—	250
No. 6	2.50	1.25	.16	.08	.00	.00	.00	22,500	6,250	14,750	—	1,875
No. 7	1.25	.63	.23	.08	.02	—	—	17,750	3,750	4,368	725	204
No. 8	.63	.63	.16	.08	.02	.02	.00	31,500	12,000	2,934	897	31
No. 9	1.25	.63	.16	.04	.00	.00	.00	35,500	11,500	1,248	117	24
No. 10	1.25	.63	.31	.16	.04	.02	.00	35,250	19,375	4,992	702	689
Average	1.05	.61	.19	.07	.02	.01	.00	29,231	9,299	7,380	852	478
								(Total—47,240)				

varied somewhat from one individual to another but, on the whole, were fairly uniform. The highest blood levels occurred one-half hour after administration and the average level, at that time, was about 1 unit per c.c. of serum. A rapid decline followed and levels generally considered to be significant were maintained for three hours only. There was no evidence of any penicillin activity at the end of six hours in any of the blood specimens. The urinary excretion paralleled these blood levels very closely. An average of 29,231 units was excreted during the first hour with a rapid decline thereafter. The total average excretion, 47,240 units or 47.24 per cent, was slightly below the figure generally reported in the literature.

## CHART II

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline (K-Salt) Penicillin (C.S.C.) in 10 c.c. Saline by Tracheal Catheter in Nine Normal Subjects

	Blood							Urinary Excretion				
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.
No. 1	.04	.04	.08	.08	.16	.04	.04	4,399	1,000	998	1,123	562
No. 2	.08	.08	.08	.08	.08	.08	.04	4,836	7,375	8,125	592	393
No. 3	.08	.16	.16	.08	.08	.08	.04	7,062	7,062	4,680	—	377
No. 4	.16	.08	.08	.08	.16	.04	.04	1,197	429	1,903	1,326	0
No. 5	.08	.16	.31	.31	.16	.04	.08	—	—	—	—	—
No. 6	.16	.16	.31	.04	.04	.02	.02	11,937	468	1,326	904	249
No. 7	.31	.31	.16	.16	.04	.04	.02	9,661	1,875	826	427	149
No. 8	.16	.16	.16	.08	.04	.04	.02	13,375	2,312	5,812	1,794	0
No. 9	.16	.16	.16	.08	.02	.02	—	12,000	1,250	5,000	4,682	200
Average	.14	.14	.17	.11	.08	.04	.04	8,060	2,721	3,365	1,545	241
									(Total—15,932)			

Nine subjects received 100,000 units of penicillin in 10 c.c. of saline by the endotracheal route (chart 2). No cough was evoked and thus, there was no loss of penicillin. The average blood level at one-half hour (0.14 unit per c.c.) was one eighth that obtained with the same dose administered intramuscularly. However, the abrupt fall in blood levels observed with intramuscular administration did not occur. On the contrary, the levels continued to increase and reached their peak (0.17 unit per c.c.) two hours after administration. At the end of three hours, the average level (0.11 unit per c.c.) was almost twice as high as the comparable intramuscular level (0.07 unit per c.c.) Significant blood levels (0.04 unit per c.c.) were

## CHART III

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline (K-Salt) Penicillin (C.S.C.) in 1 c.c. Physiological Saline by Oxygen Aerosolization in 12 Normal Subjects

	Blood					Urinary Excretion		
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	1 hr.	2 hr.	24 hr.
No. 1	.16	.16	.04	—	—	8,750	2,500	22
No. 2	.16	.08	.08	—	—	2,850	5,700	12
No. 3	.08	.08	.04	—	—	2,496	624	—
No. 4	.16	.08	.02	—	—	4,000	936	1,250
No. 5	.08	.08	.02	—	—	1,475	—	—
No. 6	.08	.04	.02	—	—	1,125	875	—
No. 7	.16	.08	.04	—	—	2,500	3,000	—
No. 8	.08	.08	.02	—	—	3,500	4,500	—
No. 9	.08	.08	.04	.02	0	3,159	2,496	1,748
No. 10	.16	.08	.04	0	0	546	507	—
No. 11	.16	.04	.02	.02	0	702	—	—
No. 12	.08	.08	.04	0	0	0	0	—
Average	.12	.08	.04	.01	0	2,592	2,113	758
						(Total—5,463)		

maintained for twice as long as with intramuscular administration (six hours). Urinary excretion correspondingly was much lower at one hour (8,060 units) and fell off less rapidly; almost an equal hourly amount was excreted from the second to the sixth hour. The total excretion of 15.9 per cent was roughly one third that obtained following intramuscular administration. These serum levels and urinary excretions are compared in figure 2.

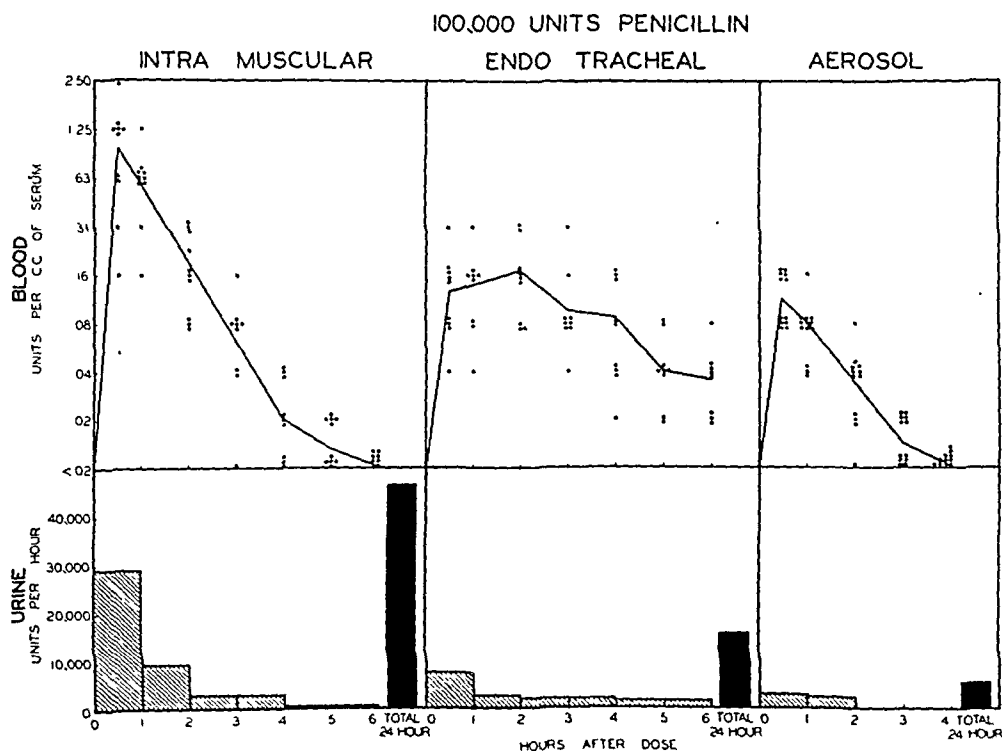


FIG. 2. Blood levels and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by various routes in normal male subjects.

Twelve patients received 100,000 units of penicillin in 1 c.c. of saline by aerosolization with the nebulizer-rebreathing bag apparatus (chart 3). The average blood level at one-half hour (0.12 unit per c.c.) parallels the corresponding level following endotracheal injection. Although the average at two hours was 0.04 unit per c.c., five of the 12 serums showed less than this therapeutically effective amount. No significant levels were encountered after two hours. Thus, although the aerosol curve reaches almost the same peak as the endotracheal curve, it drops off more quickly. Urinary excretion corresponds very closely. The total excretion averaged 5.46 per cent, approximately one third of the endotracheal excretion. These relationships are illustrated in figure 2.

#### DISCUSSION

On comparing the parenteral and endotracheal blood level curves, several facts become evident. Absorption from the alveoli is much slower than from

muscle tissue. About 75 per cent of the administered dose is absorbed and excreted from intramuscular administration during the first hour; 97 per cent of the substance is excreted within the first four hours and only traces are discernible in the blood at the end of that time. Following intratracheal administration, the peak of absorption is not reached until two hours after administration; 83 per cent is excreted during the first four hours and even at the end of six hours, levels of therapeutic significance are still found in the blood. Thus, although penicillin absorption from the lung begins almost instantly after administration, the time required to remove all the substance from the lung is about six to eight hours, while muscle tissue can be freed of penicillin almost completely within relatively few minutes.

The lungs are estimated to contain 300,000,000 alveoli with a total surface of 65 square meters and lined with capillaries whose walls are only 0.000008 cm. thick.<sup>24</sup> In view of this, an enormous absorptive capacity should be expected and our results may appear surprising. Previous studies on the absorption of fluid from the lung, however, are confirmed. In Courtice and Phipps' absorption curve of physiologic saline from the lung (figure 1) absorption took place instantly after administration, but only 36 per cent was absorbed after four hours. Their value for speed of absorption is expectedly lower than ours since 10 c.c. of fluid in a rabbit lung are equal, relatively, to 20 to 50 times the same quantity administered to man. Fatal reactions that can occur within one to two minutes after intratracheal administration of cocaine or Pontocaine<sup>18</sup> illustrate the extremely rapid absorption of small quantities of hypotonic solution. Following the intratracheal administration of adrenalin, we have observed the onset of tachycardia within 30 seconds.<sup>25</sup>

Suspension of penicillin in oil or wax, with or without Procaine, or freezing the site of intramuscular administration, slows its absorption considerably. It would seem desirable similarly to slow the absorption of penicillin from the lung, since prolonged local concentrations are very desirable. This could be accomplished if it were possible chemically to combine penicillin with a molecule sufficiently large to prevent speedy absorption as outlined above. Over four years ago, Ingraham and Gaensler<sup>26</sup> attempted to slow intramuscular absorption by combining penicillin with human albumin and globulin fractions. They demonstrated that if such chemical combination were formed, it did not affect the rate of absorption. In another part of the present study,<sup>25</sup> similar negative results were obtained when penicillin in human plasma was administered to the lungs.

Total urinary excretion, following intratracheal administration, is one third that following parenteral injection. This may be anticipated since penicillin enters the blood stream more slowly; more of it, therefore, is detoxified or inactivated and less excreted. Delayed excretion by competitive inhibition of renal tubular excretion is another example of this phenomenon.

The well maintained high blood levels suggest the intratracheal route of administration as a therapeutically desirable one. To maintain effective

blood levels by this route, injections are necessary only one-half as often as a similar dose given parenterally. Several methods of endobronchial administration of penicillin have been previously suggested. Kay and Meade<sup>27</sup> injected 250 to 10,000 units in 3.0 to 5.0 c.c. of saline by indirect laryngoscopy through a laryngeal cannula, without anesthesia, and reported favorable results in ulcerative tracheobronchitis, minimal bronchiectasis, and in preoperative treatment. Moore and Thompson<sup>28</sup> treated severe bronchiectasis with bronchial lavage and intratracheal penicillin and sulfathiazole under nupercaine anesthesia. Bobrowitz et al.<sup>29</sup> gave six bronchiectatic patients 50,000 to 250,000 units a day by the supraglottic method of instillation following cocaineization; they recorded rapid and satisfactory symptomatic improvement. Romansky<sup>30</sup> treated 12 cases of pulmonary suppurative disease with endotracheal penicillin suspended in iodized heavy oil.

We do not propose this form of treatment as a routine measure for several reasons. In order to obtain penicillin levels comparable to the ones we obtained, it is necessary to abolish the cough reflex by topical anesthesia. This not only introduces the well known hazards of topical anesthesia, but also violates an important therapeutic principle in the management of bronchopulmonary disease—maintenance of adequate cough reflex. This would be highly undesirable in the very diseases where primary application of penicillin to the tracheobronchial tree is indicated. Finally the technic of endotracheal intubation is more difficult and not as well tolerated by the patient as aerosolization.

In another study, dealing with absorption of penicillin in chronic suppurative pulmonary disease, we have consistently shown that parenterally administered penicillin does not reach the purulent sputum.<sup>31</sup> It has been the impression for some time that parenteral therapy will not penetrate the walled-off purulent cavity but will improve a surrounding pneumonitis.<sup>27, 28, 29</sup> Since the primary aim of penicillin administered directly to the lung is the production of high local concentrations, the nebulizer is the most practical tool by which the therapeutic agent can be placed at the site of the pathologic process. Endotracheal manipulation and topical anesthesia are not necessary. Most patients are easily taught to use the aerosol apparatus themselves in the hospital or at home. Furthermore, we have shown elsewhere that the amount of penicillin deposited in the lung, as evidenced by the penicillin excreted in the sputum, compares favorably with the endotracheal method. Our<sup>31</sup> experiences on the Inhalational Therapy Service and the Thoracic Surgical Service do suggest, however, that in certain special cases biotherapeutic agents may be given to great advantage by the endotracheal route. Such is the case when endotracheal intubation is necessary, primarily for other reasons, as at time of bronchoscopy or bronchography, during the course of endotracheal aspiration therapy following thoracic surgery, or in the treatment of acute atelectasis. Our experiences also suggest that when a rapid and striking reduction of sputum is necessary prior to surgery for sup-

purative disease of the lung, endotracheal therapy will produce this change in the shortest period of time.

Although aerosol therapy is not primarily designed to produce high blood levels, good concentrations can be obtained for two hours following the inhalation of penicillin. A comparison of the total urinary excretion following each of these methods enables us to calculate the portion of the aerosolized penicillin which is actually absorbed from the pulmonary epithelium. We know that no loss of penicillin occurs on endotracheal instillation in the normal anesthetized man. Of 100,000 units administered endotracheally, 15,932 units were excreted in the urine. Only 5,463 units were excreted in the urine when 100,000 units were aerosolized. We can compute the quantity of penicillin actually absorbed from the lung by the simple equation:

$$\frac{100,000}{15,932} = \frac{x}{5,463}$$

$x$ , the quantity absorbed following aerosolization, is found to equal 34,291 units. The average loss within the entire apparatus, obtained by penicillin assay of the rinsings, is 10,225 units or 10.2 per cent. The average loss obtained from assay of the saliva and mouth rinsings during aerosolization is 7,984 units or 8.0 per cent. Thus, the loss sustained before the aerosol reaches the lung is 18,209 units (18.2 per cent). Since 34,291 units are actually absorbed from the lung, the miscellaneous loss, probably mostly into the air, is 47,500 units (47.5 per cent). These various relationships are illustrated in figure 3. Roughly, then about one third of the nebulized

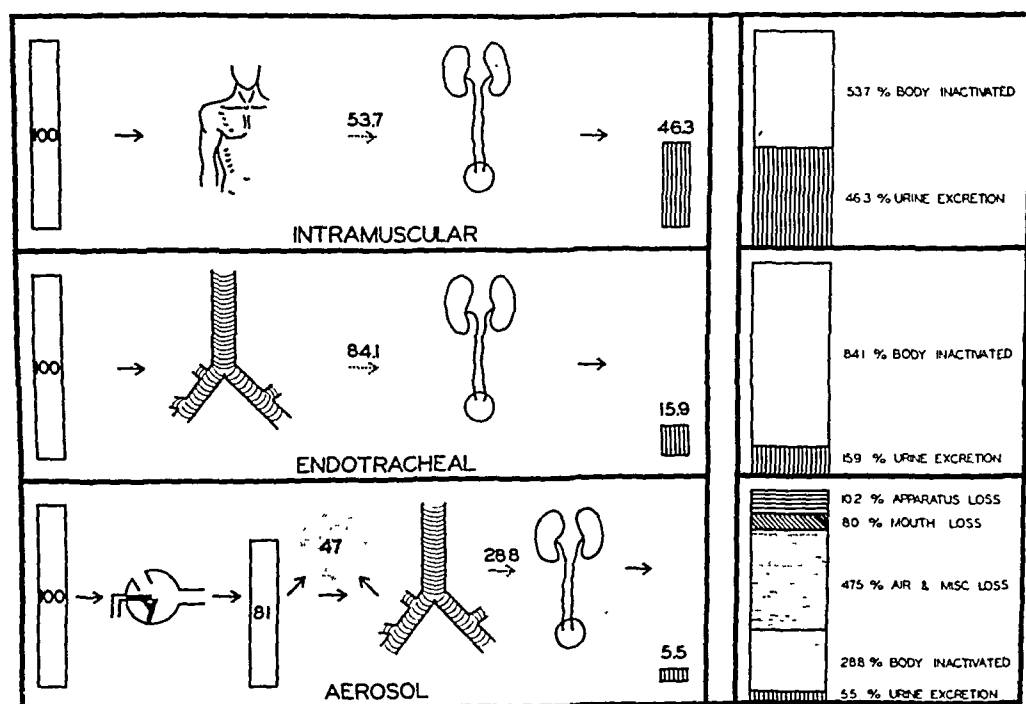


FIG. 3. Schematic representation of the fate of penicillin administered by various routes.

solution is actually absorbed by the lungs, one sixth is lost within the apparatus and the oropharynx and almost one-half is lost into the air.

### SUMMARY

1. Intratracheal administration of penicillin in saline solution in normal, anesthetized volunteers revealed that the penicillin molecule is readily absorbed into the blood stream from the alveoli. This absorption is notably slower than that following parenteral administration.

2. Blood levels following intratracheal instillation do not reach the early high peaks seen on intramuscular administration but therapeutically significant blood levels are maintained for twice as long a period of time. The average urinary excretion is 15.9 per cent, or about one third of that following parenteral administration. This suggests that the lung may act as a *depot* from which penicillin may be slowly released.

3. Intratracheal administration is suggested as a practical and advantageous method of therapy under certain, special circumstances.

4. Aerosolized penicillin solution results in early blood levels nearly as high as those obtained by endotracheal administration, but therapeutic levels are maintained for only one third as long a period of time.

5. Following aerosolization, 5.5 per cent of the administered penicillin is excreted into the urine; 10.2 per cent is lost within the apparatus, 8 per cent is lost in the oropharynx and 47.5 per cent is lost on expiration and other losses into the air. Thus one third of the aerosolized penicillin solution actually reaches the lung.

### BIBLIOGRAPHY

1. GRAESER, J. B., and ROWE, A. H.: Inhalation of epinephrine for the relief of asthmatic symptoms, *Jr. Allergy*, 1935, vi, 415-420.
2. BRYSON, V., SANSOME, E., and LASKIN, S.: Aerosolization of penicillin solutions, *Science*, 1944, c, 33-35.
3. BARACH, A. L., SILBERSTEIN, F. H., OPPENHEIMER, E. T., HUNTER, T., and SOROKA, M.: Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis and lung abscess: preliminary report, *Ann. Int. Med.*, 1945, xxii, 485.
4. SEGAL, M. S., and RYDER, C. M.: Penicillin aerosolization in the treatment of serious respiratory infections. A preliminary report, *New England Jr. Med.*, 1945, ccxxxiii, 747.
5. RICHARDS, D. W., BARACH, A. L., and CROMWELL, H. A.: Use of vaporized bronchodilator solutions in asthma and emphysema. A continuous inhalation method for severe asthmatic states, *Am. Jr. Med. Sci.*, 1940, cxcix, 225-232.
6. WINTERNITZ, M. C., and SMITH, G. H.: Preliminary studies in intratracheal therapy, collected studies on the pathology of war gas poisoning, 1920, Yale University Press, New Haven.
7. COURTICE, F. C., and PHIPPS, P. J.: The absorption of fluids from the lungs, *Jr. Physiol.*, 1946, cv, 186-190.
8. DRINKER, C. K., and HARDENBERGH, E.: Absorption from the pulmonary alveoli, *Jr. Exper. Med.*, 1947, lxxxvi, 7-18.
9. RAWSON, R. A.: The binding of T-1824 and structurally related diazo dyes by the plasma proteins, *Am. Jr. Physiol.*, 1943, cxxxviii, 708-717.



10. ABRAHAM, E. P., CHAIN, E., FLETCHER, C. M., GARDNER, A. D., HEATLY, N. G., JENNINGS, M. A., and FLOREY, H. W.: Further observations on penicillin, *Lancet*, 1941, ii, 177-186.
11. RAMMELKAMP, C. H., and KEEFER, C. S.: Penicillin: its antibacterial effect on whole blood and serum for hemolytic streptococcus and *Staphylococcus aureus*, *Jr. Clin. Invest.*, 1943, xxii, 649-657.
12. RAMMELKAMP, C. H., and BRADLEY, S. E.: Excretion of penicillin in man, *Proc. Soc. Exper. Biol. and Med.*, 1943, liii, 30-32.
13. FREE, A. H., PARKER, R. F., and BIRO, B. E.: Oral penicillin: a comparison of various modes of administration, *Science*, 1945, cii, 666-668.
14. BAYER, K. H., PETERS, L., WOODWARD, R., and VERWEY, W. F.: The enhancement of the physiological economy of penicillin in dogs by simultaneous administration of para-aminohippuric acid, *Jr. Pharmacol. and Exper. Therap.*, 1944, lxxxii, 310-323.
15. BRONFENBRENNER, J., and FAVOUR, C. B.: Increasing and prolonging blood penicillin concentrations following intramuscular administration, *Science*, 1945, ci, 673-674.
16. BEYER, K. H.: New concept of competitive inhibition of the renal tubular excretion of penicillin, *Science*, 1947, cv, 94-95.
17. BEAKEY, J. F., GAENSLER, E. A., and SEGAL, M. S.: A comparative study of various apparatus and technique for aerosol administration, *Conn. State Med. Jr.*, 1949, xiii, 855-863.
18. DERBES, V. J., and ENGELHARDT, H. T.: Deaths following the use of local anesthetics in transdermoid therapy: a clinical evaluation, *Jr. Lab. and Clin. Med.*, 1944, xxix, 478-482.
19. RAMMELKAMP, C. H.: A method of determining the concentration of penicillin in body fluids and exudates, *Proc. Soc. Exper. Biol. and Med.*, 1942, li, 95.
20. FINLAND, M., MEADS, M., and ORY, E. M.: Oral penicillin, *Jr. Am. Med. Assoc.*, 1945, cxxix, 315-326.
21. BIGGER, J. N.: Inactivation of penicillin by serum, *Lancet*, 1944, ii, 400.
22. EAGLE, H., and TUCKER, H. A.: The effect of serum on the in vitro bioassay of penicillin, 1948, in preparation. Quoted by EAGLE, H.: Speculations as to the therapeutic significance of the penicillin blood level, *Ann. Int. Med.*, 1948, xxviii, 260-278.
23. LITTLE, C. J. H., and LUMB, G.: Penicillin by mouth, *Lancet*, 1945, ccxlviii, 203.
24. HARVEY, B. C. H.: Simple lessons in anatomy, *Am. Med. Assoc.*, 1932. Quoted by PRIGAL, S. G.: Studies with medicated aerosols, 1948, xxviii, 814-828.
25. BEAKEY, J. F., GAENSLER, E. A., and SEGAL, M. S.: Pharmacodynamics of pulmonary absorption in man. II. The influence of various diluents on aerosol and intratracheal penicillin. To appear in November 1949 issue, *Ann. Int. Med.*
26. INGRAHAM, F. D., and GAENSLER, E. A.: Unpublished data, 1944.
27. KAY, E. B., and MEADE, R. H., JR.: Penicillin in the treatment of chronic infections of the lungs and bronchi; analysis of 93 cases, *Jr. Am. Med. Assoc.*, 1945, cxxix, 200-204.
28. MOORE, F. H., and THOMPSON, J. W.: Intrabronchial instillation of penicillin or sulfonamide solution, with bronchial lavage, in the treatment of severe bronchiectasis, *Naval Med. Bull.*, 1945, xlv, 1097-1103.
29. BOBROWITZ, I. D., EDLIN, J. S., BASSIN, S., and WOOLEY, J. S.: Penicillin in the treatment of bronchiectasis, *New England Jr. Med.*, 1946, ccxxxiv, 141-147.
30. ROMANSKY, M. J., DUGAN, D. J., and RITTMAN, G. E.: Penicillin in iodized oil for instillation into the lungs, *Science*, 1945, cii, 255-256.
31. GAENSLER, E. A., BEAKEY, J. F., and SEGAL, M. S.: The relative effectiveness of parenteral, intratracheal and aerosol penicillin in chronic suppurative disease of the lung, *Jr. Thorac. Surg.*, 1949, xviii, 546-560.

# THE HEREDITY OF GOUT AND ITS RELATIONSHIP TO FAMILIAL HYPERURICEMIA \*

By ROBERT M. STECHER, M.D., F.A.C.P., A. H. HERSH, Ph.D., and  
WALTER M. SOLOMON, M.D., F.A.C.P., *Cleveland, Ohio*

DESPITE the fact that gout has long been recognized as a hereditary disease and that much study has been devoted to this phase of the problem, the exact pattern of inheritance has not been clearly identified. It seemed likely that a broader concept of the disease and the application of modern methods of genetic investigation to readily available data might add much to our understanding of the disease. The present study was undertaken in the hope that these potentialities might be realized.

The most striking features of gout have always been associated with the joint phenomena. Characteristically these consist of a series of sudden, acute, painful attacks of arthritis involving with decreasing frequency the joints of a big toe, the feet, the knees and the hands. The joints may become affected overnight and are greatly swollen, very red, markedly tender and hot. There is often fever and leukocytosis. The attacks subside spontaneously in days to months and complete recovery is the rule. Only as a result of repeated attacks and after many years does chronic joint damage with deformity occur. The deposition of uric acid crystals as tophi in the skin about the ears, or in bones about the joints and resulting in punched-out areas seen by roentgen-ray, are the pathognomonic lesions of the disease. They appear only late in the disease, if at all, and they escape detection entirely in many victims. Because the joint manifestations of gout characteristically occur only in middle or later life and because they are often atypical and cannot be correctly identified, many affected members of the gouty family are not recognized and the genetic pattern is rarely complete.

Gouty patients have an abnormally high level of uric acid in the blood, one manifestation of the faulty uric acid metabolism which is characteristic of the disease. Hyperuricemia is present whether the patient is having gouty attacks or not and this abnormality has been observed in patients before they developed clinical gout. A substantial proportion of the near relatives of gouty people have been found to have hyperuricemia. This suggested that the genetic pattern and the mechanism of inheritance of familial hyperuricemia might be recognized and that analysis of this trait could yield valuable information about the heredity of gout. The present study, therefore, is one of the genetics of familial hyperuricemia and for this purpose familial hyperuricemia is considered to have exactly the same significance as clinical gout.

\* Received for publication April 21, 1947.

From the Department of Medicine, School of Medicine at City Hospital and the Department of Biology, Western Reserve University.

No attempt will be made to review the literature on the subject. Several recent papers<sup>1,2</sup> refer to previous statements on the subject. The present study considers idiopathic hyperuricemia as genetically related, if not even identical, with gout. Folin<sup>3</sup> noted idiopathic hyperuricemia in the brother of a gouty patient as did also Jacobson.<sup>4</sup> Talbott<sup>5</sup> studied 136 relatives of 27 gouty patients. He found that 34 of them, or 25 per cent, had serum uric acid levels which were abnormally high. He states that an increased concentration of urate in the body is the most significant factor in gout and that this finding in one fourth of the apparently normal relatives indicates that the manifestation is a familial one which may be present at birth or shortly after. Although the sexes were about evenly divided in the 136 relatives (58 per cent males), of the 34 affected ones, 27, or 80 per cent, were males. Four of the 34 affected relatives were under 20 years of age, the youngest being 14 years. Smyth and Freyberg<sup>6</sup> reported two remarkable gouty families. In one a gouty father and normal mother had three gouty sons and a normal daughter. In the second family the same combination of parents had four normal children but two of the three sons had abnormally high levels of serum uric acid.

The diagnosis of gout in the present series was based upon a summation of clinical and chemical evidence often after observation extending over varying periods of time. Factors considered included the story of typical attacks of gout interrupted by complete remissions for months or years and the finding of hyperuricemia. Punched-out areas in bones and other tophi were found in only a few cases.

In this study, once a patient had been accepted as gouty, it was decided that every one of his tested relatives would be included for consideration and classified as being normal or having familial hyperuricemia. A definite level of serum uric acid demarcation between normal and affected was chosen based upon our experience despite the obvious fact that such an exact distinction would of necessity be arbitrary and that repeated observations on the same individual might fall on different sides of the line.

Certain other well known conditions influencing the level of blood uric acid had to be considered. Hyperuricemia in the absence of gout is sometimes found in kidney insufficiency, lobar pneumonia and leukemia. A high fat diet causes a retention of uric acid with an elevation of its blood level. Blood uric acid can be lowered by proper treatment of gouty patients. Large doses of cinchophen or aspirin were found to reduce blood uric acid drastically.

Although a high level of uric acid in the blood has been recognized as a sign of gout since Garrod<sup>7</sup> announced it in 1848, no definite upper limit of normal or lower limit of gout has ever been established. Jacobson,<sup>4</sup> following a suggestion made years ago by Folin, used serum separated out of clotted blood instead of whole blood for uric acid determination. This procedure proved to be much more reliable than former methods because a sharp line of demarcation was found between normal and gouty individuals in most in-

TABLE I  
Serum Uric Acids  
1272 determinations on 1,162 individuals

	Number of Individuals	Number of Determinations	Determinations below 6.5 mg.	Determinations 6.5 mg. or over	Average
A. Gouty families					
1. Index cases	41	77	3	74	8.12
2. Hyperuricemia	17	23	1	22	7.37
3. Normal relatives	120	124	123	1	
4. Spouses of gout	23	24	22	2	
Total	201	248	149	99	
B. General population					
5. Normal kidney function	878	927	893	34	
6. Nitrogen retention	83	97	72	25	
Total	961	1,024	965	59	
Grand total	1,162	1,272	1,114	158	

stances, 94 per cent of 177 determinations on 21 gouty subjects being over 7 mg. per 100 c.c. Among 100 non-gouty subjects there were only three determinations above 6 mg.

Because of the importance of recognizing a definite level between hyperuricemia and normal it seemed desirable to determine the dividing line to be used in this study from our own experience of 1,272 tests. These included 248 tests on 41 gouty patients and 159 of their relatives or spouses and 1,024 tests done routinely on 961 patients on the medical wards of Cleveland City Hospital, shown in table 1. All determinations used in this study were made by one individual using Benedict's direct method, and read with a Klett Electric Colorimeter on serum separated from clotted blood. Specimens were collected under oil without regard to fasting.

Table 2 shows the distribution of values in various classes of individuals. Examination of this table shows a natural division of high and low levels

TABLE II  
Serum Uric Acid Levels  
Distribution of 1,272 determinations

	0- 1.9	2.0- 2.4	2.5- 2.9	3.0- 3.4	3.5- 3.9	4.0- 4.4	4.5- 4.9	5.0- 5.4	5.5- 5.9	6.0- 6.4	6.5- 6.9	7.0- 7.4	7.5- 7.9	8.0- 8.4	8.5- 8.9	9 +
A. Gouty families																
1. Index cases									1	2	8	13	14	12	15	12
2. Hyperuricemia									1	1	7	7	3	3		2
3. Normal relatives			6	11	21	22	16	25	18	4	1					
4. Spouses of gout		1	3	2	2	3	6	2	2	1	1		1			
Total 248		1	9	13	23	25	22	27	21	8	17	20	18	15	15	14
B. General population																
5. Normal kidney function	54	65	106	136	153	162	80	70	42	25	12	5	8	1	2	6
6. Nitrogen retention	2	1	5	7	11	11	12	6	11	6	4	7	3	2	3	6
Total 1,024	56	66	111	143	164	173	92	76	53	31	16	12	11	3	5	12
Grand total 1,272	56	67	120	156	187	198	114	103	74	39	33	32	29	18	20	26

between 6.4 mg. and 6.5 mg. A marked preponderance of determinations in gouty or hyperuricemic individuals fall to the right of this line. A marked preponderance of tests of non-gouty individuals fall to the left of this line. Thus in 77 tests upon 41 patients with gout, all but three are 6.5 mg. or more per 100 c.c. Of 23 determinations on 17 relatives considered to have hyperuricemia, only one was below 6.5 mg. In these two groups of hyperuricemic individuals, uric acid levels were above 6.5 mg. in 96, or 96 per cent of the tests.

Of 1,024 tests on 961 patients on the medical wards, 965 were below the level of 6.5 mg. Of the 59 above this value, 25 were on patients with nitrogen retention, a condition expected to produce hyperuricemia. Thus, only 34 or 3 per cent of the tests showed an unexplained value above 6.5 mg. which might have been due to idiopathic hyperuricemia. As a result of these observations, and in the absence of evidence to the contrary, a serum uric acid level of 6.5 mg., or over per 100 c.c., was tentatively accepted as hyperuricemia or proof of gout.

The validity of this line of distinction between normal and hyperuricemia was tested statistically. A group of 294 normal females of the hospital population gave a mean uric acid level with the standard error of  $3.63 \pm 0.06$  mg. per 100 c.c. with a standard deviation of  $1.06 \pm 0.04$  mg. per 100 c.c. The mean with its standard error for a similar group of 296 normal males was  $3.95 \pm 0.06$  mg. uric acid per 100 c.c. with a standard deviation of  $1.15 \pm 0.04$  mg. per 100 c.c. The difference in the means with its standard error is  $0.32 \pm 0.08$ , a significant difference which one could expect as a result of random sampling only about once in more than 15,000 trials. The average uric acid concentration for the males is 1.088 times that for the females, which curiously enough agrees very closely with the differences between the sexes in physical stature as determined many years ago by Galton, and also with the difference in the figure usually taken as the average cranial capacity, 1,200 c.c. for females, 1,300 c.c. for males.

To cut off the normal curve in the plus direction at two times the standard deviation brings the upper level of normality for males to 6.25 mg. and allows about one man in 50 to stand above that level who still might be regarded as normal. If it is desired to reduce this figure to one in 100, then the level of demarcation in round figures could be placed at 6.50 mg., 2.22 times the standard deviation above the mean. A similar estimate for females is 5.98 mg. It is interesting to note that in the sample of 294 normal females there were two who showed 6.0 mg. or more per 100 c.c. These values, 6.5 mg. for males and 6.0 mg. for females, are then taken as the upper levels of normality for purposes of this study.

The present genetic study is based on 44 primary index cases, their 17 hyperuricemic or gouty relatives, and 120 normal relatives. There are also 23 spouses. The group consists of 203 individuals almost equally divided as to sex with 104 males and 99 females. Twelve of the primary index cases had no available relatives and were included only to broaden the ob-

TABLE III  
Pedigrees of 40 Gouty Families

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
1. M. A. male (63) 8.0 8.0		(62) 2.9				(39) 4.4 (38) 5.4 (35) 5.9 (31) 5.9 (27) 4.9 (23) 5.1	(40) 3.9
2. C. B. male (65) 10.8 9.5				(70) 5.2			
3. J. B. male (50) 6.5			(72) 4.2		(41) 2.6		
4. G. C. male (62) 7.8 7.2 7.8 7.3		(58) 5.6				(36) 5.2	(28) 4.6
5. E. C. male (61) 7.6 8.1					(64) 3.7 (62) 4.3 (60) 3.7 (56) 5.1		(38) 5.1
6. D. D. male (70) 8.4 8.8						(48) 4.1 (38) 4.6 (32) 5.8 (25) 7.2	(36) 5.4
7. L. D. male (48) 7.3				(66) 5.4	(51) 7.1		
	8. B. B. female (51) 7.1	(45) 6.0				(12) 4.8	(30) 3.7 (28) 4.8 (26) 4.1 (25) 4.7 (24) 4.5 (22) 4.8 (19) 4.8 (16) 4.3
9. F. D. male (46) 7.0 5.5			(74) 4.4				

TABLE III—Continued

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
10. H. D. male (50)			(68) 5.4		(52) 6.6	(23) 5.0	
11. H. D. male (50) 7.3			(82) 4.9	(55) 4.1 (44) 5.4 (38) 4.3	(61) 3.5 (58) 4.7 (46) 4.4		
12. G. F. male (71) 6.9 8.0					(68) 8.2		
	13. Mrs. W. female (68) 6.1 6.6 8.2	(70) 5.0				(44) 6.3 (31) 6.8	(47) 5.5
14. D. H. male (61)		(68) 4.6		(69) 5.9		(40) 6.5 (38) 5.4 (34) 4.3	(38) 3.4 (31) 5.1 (30) 4.3 (28) 3.4
15. J. H. male (52) 7.1 9.0		(50) 6.9 7.7	(72) 5.1	(40) 7.4			(27) 2.7 (25) 4.3 (21) 3.9 (18) 3.9
	16. G. H. male (40) 7.2 7.4	(40) 2.4					(12) 2.6 (10) 3.6
17. P. J. male (50) 8.5 9.8		(49) 3.8				(16) 5.4	
18. J. K. male (49) 8.3		(47) 4.5			(63) 5.4 (47) 3.5	(12) 4.5	(27) 3.8 (23) 3.2 (19) 4.3
19. S. K. male (27) 7.3			(49) 2.8	(18) 5.5	(11) 3.3		
20. T. K. male (67) 8.3 7.6 7.5 7.5		(63) 4.8		(75) 3.7 (60) 5.8			(45) 4.2 (41) 3.4

TABLE III—*Continued*

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
21. O. K. male (53) 8.9		(55) 4.6		(61) 6.1		(14) 4.0	(32) 4.4
22. E. L. male (50) 9.2		(48) 5.2	(81) 4.8	(52) 5.3		(19) 5.7	(17) 4.9
23. A. L. male (62) 8.5 9.2 8.5				(48) 7.5			
24. O. L. male (68) 7.2 8.1		(66) 3.3					(39) 3.0 (34) 3.6
25. S. N. male (43) 6.6 6.3		(40) 2.9	(65) 4.5	(37) 5.6			(13) 4.4
26. J. P. male (58) 7.3 8.4 8.7 10.7			(80) 9.4 8.3	(55) 3.4 (44) 3.4	(49) 3.9 (42) 2.8		
27. J. P. male (66) 7.7 7.2 9.0 7.6				(70) 6.1 (65) 5.6		(42) 5.5 (35) 5.8	(41) 3.7
28. E. S. male (46) 8.5		(44) 4.8	(69) 9.3	(45) 7.0		(19) 5.7	(16) 4.7
	29. Mrs. S. female (69) 6.7 9.3				(71) 6.9 (65) 7.1		
	30. Mrs. B. female (65) 7.1	(80) 4.5				(45) 7.6 (40) 8.1 (38) 5.2	
	31. Mrs. B. female (71) 6.9						(48) 5.3 (31) 5.2



TABLE III—*Continued*

Index Cases		Spouse	Mother	Brother	Sister	Son	Daughter
Primary	Secondary						
	32. R. B. male (40) 8.1	(38) 3.8				(20) 3.9	
	33. F. B. male (45) 7.6	(42) 2.8				(18) 3.9	(20) 2.9
34. S. S. male (48)		(50) 4.1					(32) 4.0 (30) 5.0 (27) 3.9 (24) 3.1
35. H. S. male (30) 8.7 7.6 8.0				(33) 7.8 (27) 5.3	(13) 3.5		
36. J. V. male (48) 8.1		(40) 4.2)			(44) 3.1		(28) 3.5
37. J. V. male (64) 8.1 8.5						(34) 4.1	
38. G. W. male (46) 9.5		(45) 5.6				(28) 6.7	(28) 4.4 (24) 3.8
39. M. W. male (32) 8.8 6.2			(62) 5.5	(30) 5.1 (26) 5.9	(38) 3.1 (34) 3.4 (22) 4.2 (20) 3.8		
40. S. W. male (61) 7.0						(28) 5.1	

One father of an index case was seen in family No. 15, (82) 4.1, 2.7. Twelve additional index cases (those without relatives) were as follows: (73) 6.9; (72) 8.7; (56) 8.7; 7.1, 7.8, 6.6; (44) 7.4; (70) 6.9; (61) 8.6, 11.2, 7.7, 7.6; (65) 8.8; (61) 7.6, 9.4; (53) 6.5; (43) 9.1; (51) 6.9; and (58) 8.5.

servations on serum uric acid levels of gouty people. There are thus 32 primary gouty families. Eight of the 16 hyperuricemic or gouty relatives were made secondary index cases in order to include their children in the study. There is then a total of 52 index cases, 40 of which serve as starting points for the study of groups of relatives. Full data of the 40 families are

presented in table 3. This shows the age when seen and sex of each index case, the age, sex and relationships of each relative examined and all of the serum uric acid determinations done on the entire group in the course of this study. The spouses are included so that the reader may reconstruct the pedigrees if he wishes. Each secondary index case is a duplication having been shown before in a previous family. Initials are given only for index cases. The relationship is shown by the column, age is given in brackets. The relatives we have considered affected are indicated by underlining.

Of the 44 primary index cases, all had gout, all were male, all had high serum uric acid levels, save three men with undoubted gout, known to have had a high level of whole blood uric acid but who died before this study was started, and whose families were known and available to us. Seventy-seven serum uric acid determinations on these 41 index cases averaged 8.12 mg. per cent. The lowest determinations were 5.5, 6.2 and 6.3 mg. per cent, these three being all that fell below 6.5 mg. each in an individual who had other determinations above this level.

TABLE IV  
Hyperuricemia in Relatives

	Mother	Brother	Sister	Son	Daughter
Number examined	11	23	24	33	45
Number affected	2	4	5	5	0
Proportion affected (%)	18	17	21	15	0

Having the above data available, it seemed desirable to investigate the proportions of involvement among different degrees of relationship. The results are shown in table 4. Because of the known preponderance of gout in males it seems desirable to consider each sex separately. Inquiry was made concerning all the parents. Of 88 parents of 44 primary index cases only 12 were available for examination. These included the mother in 11 families. Twice she was found to have hyperuricemia but never gout. One father (of the index case J. H., family No. 15) examined was thought to have gout clinically but he showed a normal uric acid level twice. One other father was reported to have had gout but he has not been included in our computations. Thus 2 of 12 parents or about 17 per cent of those examined were found to have hyperuricemia. No attempt was made to analyze involvement of parents of the hyperuricemic relatives because they had one involved parent by definition.

Of the primary index cases, 16 had brothers. These 16 men had 23 brothers of whom 4 or 17 per cent had hyperuricemia. Twelve primary index cases had 22 sisters. One other person, the mother of an index case, had hyperuricemia and her 2 sisters had hyperuricemia, one of them gout. Of 24 sisters then, 5 or 21 per cent had hyperuricemia. The incidence of hyperuricemia in the siblings of gouty people is about 20 per cent and there is no significant sex difference.

TABLE V  
Classification According to Parents

Family	Father	Mother	Total Sons	Affected Sons	Total Daughters
Both Parents Affected					
15	Gout	H.U.A.	0	0	4
Father Affected					
6	Gout	Unknown	4	1	1
38	Gout	Normal	1	1	2
1	Gout	Normal	6	0	1
14	Gout	Normal	3	1	4
27	Gout	Unknown	2	0	1
18	Gout	Normal	1	0	3
4	Gout	Normal	1	0	1
21	Gout	Normal	1	0	1
22	Gout	Normal	1	0	1
28	Gout	Normal	1	0	1
32	H.U.A.	Normal	1	0	0
33	H.U.A.	Normal	1	0	1
10	Gout	Unknown	1	0	0
17	Gout	Normal	1	0	0
37	Gout	Unknown	1	0	0
40	Gout	Unknown	1	0	0
34	Gout	Normal	0	0	4
24	Gout	Normal	0	0	2
20	Gout	Normal	0	0	2
36	Gout	Normal	0	0	1
25	Gout	Normal	0	0	1
5	Gout	Unknown	0	0	1
16	H.U.A.	Normal	0	0	2
Mother Affected					
8	Normal	H.U.A.	1	0	8
29	Unknown	H.U.A.	2	2	0
30	Normal	H.U.A.	3	2	0
26	Unknown	H.U.A.	3	1	2
13	Normal	H.U.A.	2	1	1
31	Unknown	H.U.A.	0	0	2
Both Parents Normal					
15*	Normal	Normal	2 40	2 11	0 48

\* Refers to parents of index case.

Thirty-three sons from 19 families were studied. The father was the index case 16 times, 14 times because he had gout, twice because he had hyperuricemia. The mother was the index case 3 times, once with gout, twice with hyperuricemia. Of 33 sons, 5 or 15 per cent had hyperuricemia. Of 45 daughters, not one was found affected. These 45 daughters came from 22 families. The father was the index case 19 times, the mother three

times. Seventeen of the fathers had gout, two had hyperuricemia. All the mothers had hyperuricemia.

Study of table 5 shows the proportion of involved offspring from various combinations of involved and normal parents. In only one family, No. 15, were both parents involved, the father with gout, the mother with hyperuricemia. The four daughters from this union were normal. There were no sons. In nine families sons were born of gouty fathers and normal mothers (Nos. 38, 1, 14, 18, 4, 21, 22, 28, 17). In two other families the father had hyperuricemia without gout, the mother was normal (Nos. 32, 33). These families had 18 sons and 16 daughters. In only one family of this known combination was an affected son produced (No. 38). In five other families with gouty fathers, but mothers unknown (Nos. 6, 27, 10, 37, and 40), there were nine sons and two daughters with only one son affected (No. 6). There were six families with mothers with hyperuricemia and three normal fathers (Nos. 8, 30, 13) and three fathers untested (Nos. 28, 26, 31). In family 26 reference is to parents of the index case. There were 11 sons in these families of whom six were affected. Four of these families had daughters (Nos. 8, 26, 13, 31), a total of 13, all normal. Both parents of index case No. 15 were normal and both sons, their only children, were affected. In eight other families, the mothers were normal and fathers unknown (Nos. 39, 3, 9, 10, 11, 19, 22, and 25). These eight families will not be discussed because the possibilities of an affected father cannot be excluded.

In six families with gouty fathers (Nos. 34, 24, 20, 36, 25, 5) and another family with hyperuricemic father (No. 16) and the mothers normal or unknown, there was a total of 13 daughters, all normal, but no sons.

It is seen that in every instance where something was known about at least one parent, not a single affected daughter among 48 was found although there were 10 affected of 40 sons. Furthermore, the degree of involvement in the parents was no reliable index as to how they would transmit the abnormality. Two affected parents had only four daughters, all unaffected. Two normal parents with only two sons had both affected. Of 23 families with the father involved but mother normal or unknown there was a total of 27 sons, of whom only one each in two different families was affected. There were 31 daughters in these families, only three of whom were in the two families with affected sons. There were six families with affected mothers and normal or unknown fathers. These families produced 11 sons of whom six were affected. Four of these six families produced affected sons. These four families with six affected sons produced only three daughters. Thus with the father affected, only two of 27, or 8 per cent of the sons were affected. With mothers affected, six of 11, or one-half of the sons were affected. The effect of sex was marked. The apparent immunity of daughters is not so convincing when we realize that only 6 of 21 families having sons and with one parent involved proved that they could transmit hyperuricemia to a son. Six daughters only sprang from these six

families compared to 15 sons, eight of whom were affected. Forty-two daughters sprang from 23 families which demonstrated no ability to transmit hyperuricemia.

Table 6 is a study of sibships. The constitution of the parents is given when known. This may seem like a duplication of the previous table but the classification is according to involvement or not of a sibling. It includes all of the sibships in the previous table, as well as others in which nothing

TABLE VI  
Classification of Families According to Sibships

Family	Total Sons	Affected Sons	Total Daughters	Affected Daughters	Fathers	Mothers
Sibships with Affected Brothers						
15	2	2	0	0	Normal	Normal
28	2	2	0	0	Unknown	H.U.A.
30	3	2	0	0	Normal	H.U.A.
26	3	1	2	0	Unknown	H.U.A.
13	2	1	1	0	Normal	H.U.A.
39	3	1	4	0	Unknown	Normal
6	4	1	1	0	Gout	Unknown
38	1	1	2	0	Gout	Normal
3	1	1	1	0		
5	1	1	4	0		
10	1	1	1	1		
12	1	1	1	1		
18	1	1	2	0		
36	1	1	1	0		
35	3	2	1	0		
7	2	1	1	1		
19	2	1	1	0		
21	2	1	0	0		
23	2	2	0	0		
25	2	1	0	0		
22	2	1	0	0		
20	3	1	0	0		
27	3	1	0	0		
11	4	1	3	0		
Sibships with Normal Brothers						
1	6	0	1	0	Gout	Normal
14	3	0	4	0	Gout	Normal
27	2	0	1	0	Gout	Unknown
8	1	0	8	0	H.U.A.	Normal
18	1	0	3	0	Gout	Normal
4	1	0	1	0	Gout	Normal
21	1	0	1	0	Gout	Normal
22	1	0	2	0	Gout	Normal
28	1	0	1	0	Gout	Normal
32	1	0	0	0	H.U.A.	Normal
33	1	0	1	0	H.U.A.	Normal
10	1	0	0	0	Gout	Unknown
17	1	0	0	0	Gout	Unknown
37	1	0	0	0	Gout	Unknown
40	1	0	0	0	Gout	Unknown

TABLE VI—*Continued*

Family	Total Sons	Affected Sons	Total Daughters	Affected Daughters	Fathers	Mothers
Sibships with Affected Sisters						
29	0	0	3	3	Unknown	Unknown
10*	1	1	1	1	Unknown	Unknown
12*	1	1	1	1	Unknown	Unknown
7*	2	1	1	1	Unknown	Unknown
Sibships with Unaffected Sisters Only						
15			4	0	Gout	H.U.A.
34			4	0	Gout	Normal
24			2	0	Gout	Normal
16			2	0	H.U.A.	Normal
36			1	0	Gout	Normal
25			1	0	Gout	Normal
5			1	0	Gout	Unknown
31			2	0	H.U.A.	Unknown

\* Shown in table of Affected Sons.

is known of the parents. According to table 5, there were 24 sibships with at least one affected brother. In eight of these the constitution of one or both parents is known. These 24 sibships had 51 males of whom 29 or 57 per cent were affected. Of the 24 families 15 or 62 per cent had daughters, 26 in number, of whom one each in three sibships was affected (Nos. 10, 12, 7). Another 15 sibships had 23 males, all normal. Each of these families had an affected parent or it would not have been included in the study. Ten of the sibships had 23 females, all normal. Four families had affected sisters, three mentioned above (Nos. 10, 12, 7) and another (29) with three sisters all involved. Eight additional sibships without sons had 17 daughters, all normal.

Involvement of women with hyperuricemia was rare but significant. Of the four sibships with involved women, a total of six women were examined and all found involved. Of four brothers of these women, three were found affected. Nine of the 10 people in these four sibships involving affected women were affected. Only two other affected females were discovered in the entire study, a spouse (No. 15) and a mother (No. 26). Of the eight women with hyperuricemia, only one could possibly be considered to have clinical gout.

Consideration of the data of table 3 and table 5 is sufficient to show that the inheritance of hyperuricemia exhibits certain irregularities. This is emphasized more clearly by an examination of the pedigrees of several of the more significant families. Figure 1 shows in pedigree form the data for families 15 and 16, while figure 2 gives the pedigree for the related families 28, 29, 30, 31, 32 and 33 of table 3.

In figure 1, neither parent in generation I has hyperuricemia, but both sons show the trait. This in itself would be an indication that the trait is a recessive and that the parents are both heterozygotes. But in the same pedigree in generation II the first set of parents both show the trait but their four daughters are not affected. Obviously, if the trait were a simple autosomal recessive all these daughters should show the trait. Gout in women is known to be rare. In the entire study 62 individuals showed hyperuricemia of whom only eight were women. Of the affected group, 13 per cent were women and 87 per cent were men. Because of the fact that seven times as many men as women are affected, this pedigree might be satisfactorily regarded as that of a recessive in which there was considerable lack of penetrance in the female.

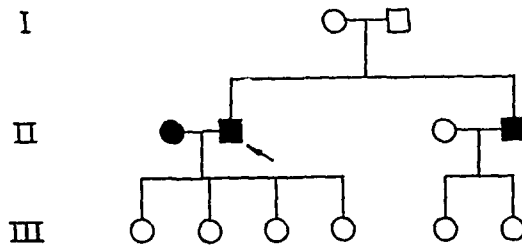


FIG. 1.

In figure 2 we have a remarkable family of three affected sisters. The family of the oldest sister consists of two normal daughters; the second sister has two sons, both affected; the third sister has three sons, two of whom are affected. This pedigree has the appearance of a typical dominant. If it were recessive, both parents of the three sisters and the husbands of the two younger sisters would need to be heterozygotes and so would the spouses of all of the gouty people who begot affected children. Because of the low incidence of hyperuricemia in the population, the probability of this seems to be very slight. It is more probable that the spouses were homozygous for a normal recessive gene and the sisters themselves as well as other gouty

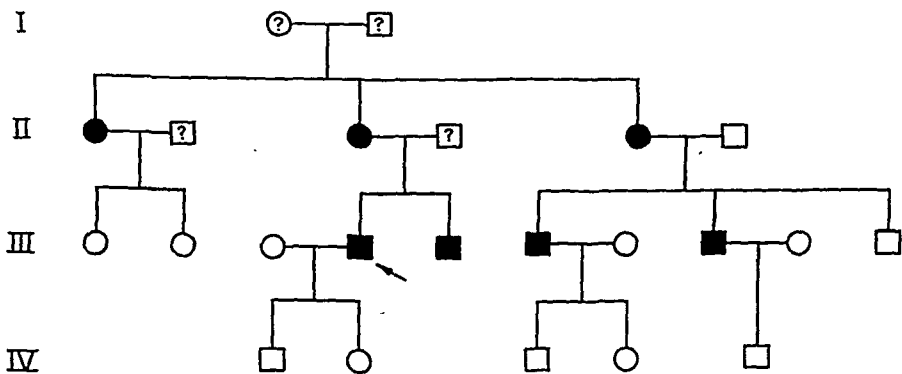


FIG. 2.

parents with affected offspring were heterozygous for a dominant gene which acts irregularly in many families. It is clear that a dominant gene which lacks penetrance can resemble a recessive in some pedigrees.

These two pedigrees, taken in conjunction with the other families of table 3, justify the conclusion that the genetic peculiarities of hyperuricemia are mainly the expression of an autosomal dominant gene which lacks penetrance in both sexes, but with a much lower penetrance in the female than in the male, perhaps about one-seventh as much.

Gout is a disease in which the average age of recognition is in the middle or later life and the lack of penetrance observed might be dependent upon the low age of the population studied. The relationship of age to serum uric acid level was tested by computing the coefficient of correlation ( $r$ ). The determination was made for each sex separately. The value of  $r$  with its standard error was found to be  $+0.088 \pm 0.129$  for male relatives of gouty people. This shows complete lack of correlation indicating that there is no significant increase of the serum uric acid in males after the age of 20. No alteration in penetrance is to be expected with advancing years. The finding in regard to women is quite different. Here  $r$  was found to be  $+0.44 \pm 0.09$ , a degree of correlation which is definitely significant. A marked difference is thus revealed between men and women. Inspection of the correlation table shows that every woman with hyperuricemia was over 50 years of age, a fact which suggests that normal menstrual function inhibits the development of idiopathic hyperuricemia.

Whether the level of serum uric acid is definitely established for men at adolescence or earlier in childhood is at present unknown. The present series included only eight males below the age of 20, so that our observation on this point is limited. Talbott, however, observed hyperuricemia in four males under the age of 20, the youngest being 14. His observations differed from ours also regarding the age of females. Among the relatives of gouty patients, he records seven hyperuricemic women all under the age of 42, the youngest being 21.

From the above considerations we tentatively conclude that hyperuricemia is an autosomal dominant with low penetrance in both sexes, but considerably lower in the female than in the male. Since it is desirable wherever possible to put the conclusion to the numerical test, even when the data for making such a test may be somewhat inadequate and inconclusive, we have assembled the pertinent data from table 3 in table 7. It is well known that in analyzing human genetic data a correction must be made for small family size. When families are small, certain families of the proper genetic constitution but having several unaffected offspring will go unrecognized and therefore uncounted. The observed affected offspring will consequently be more than the theoretically expected number.

Hogben<sup>8</sup> has published tables of corrective factors for families of different size. These tables are for testing ratios in fraternities for genes with



full penetrance. The test in table 7 is for males only. The fraternities used from table 3 are those with more than one son, and in which at least one son was affected. The test is made for a 1:1 ratio, since if one son is affected it follows that one parent was at least heterozygous for the dominant gene with the other parent homozygous for the normal recessive allele. Because of the low incidence of hyperuricemia in the population there are not likely to be many homozygous dominants or matings where both parents are heterozygous. Twenty fraternities with more than one son and with at least one son affected are available (families 2, 6, 7, 11, 13, 15, 19, 20, 21, 22, 23, 25, 26, 27, 28, 30, 35 and 39 with one sibship, 14 with 2). In these 20 fraternities there are 51 men, 26 of whom are affected. After correction for small family size the number expected with its standard error is  $30.9 \pm 2.7$ . This shows a remarkably good agreement considering the lack of full penetrance. In fact, if the provisional conclusion that hyperuricemia is an autosomal dominant with lack of full penetrance be accepted, then the results may be used to estimate the penetrance. That is, 26 are observed affected where 31 are expected, showing that on this basis penetrance of the gene is about 84 per cent in heterozygous males. Although the 203 individuals in the study series were equally divided as to sex, there were 54 hyperuricemic males compared to eight hyperuricemic females, a ratio of 7 to 1. Penetrance in women therefore seems to be about one-seventh as high as in men or about 14 per cent.

TABLE VII

Comparison of Affected Men with Theoretical Expectancy on Basis of 1:1 Ratio.  
Corrected for Family Size

Number of Siblings	Number of Families	Total Number of Men	Affected Men	Factor	Expected Affected
2	11	22	15	1.333	14.663
3	7	21	9	1.715	12.005
4	2	8	2	2.134	4.268
	20	51	26		30.936

When the mother is the parent affected, there seems to be a stabilizing effect on the action of the gene so that penetrance in the sons seems to be almost complete. Of six sons born of affected mothers, three had hyperuricemia compared to 27 sons of affected fathers, only three of whom had hyperuricemia. Although the sample is small, it appears that the higher penetrance in sons of affected mothers may be due to a maternal effect, some influence on the cytoplasm of the egg at the time of maturation, or during the uterine history.

In conditions occurring predominantly in males the possibility of sex linkage is always suggested. In sex linkage the gene for the suspected trait is carried on the X chromosome which males inherit from their mother.

With mothers affected all sons become involved. Fathers do not transmit to their sons. This situation is approached in this series in that six of eight sons of five affected mothers had gout. Fathers, however, do not transmit sex-linked characters to their sons but only produce carriers of their daughters. In this series three fathers transmitted gout to their sons, table 3, Nos. 7, 14, 38. Smyth and Freyberg<sup>6</sup> described two similar instances. The data do not support the theory that gout or hyperuricemia are sex-linked characters.

The possibility that hyperuricemia might be a recessive trait was tested in the following way: When one parent shows a trait and some of the children are affected, the other parent may be normal if the trait is dominant. If the trait be recessive, however, the phenotypically normal parent must be heterozygous or affected children will not appear. It is obvious that there must be a sufficient reservoir of heterozygotes in the population to give a reasonable probability that the required number of matings may occur with random mating. In other words the genetic analysis of the data of the pedigrees must be consistent with the gene frequencies in the population.

Since about one-eighth of the relatives of gouty people were found to have unsuspected hyperuricemia it seemed reasonable to suppose that this trait might be observed in a discoverable proportion of the general population selected at random. In an effort to test this supposition, routine serum uric acids were done on patients on the medical wards at City Hospital, care being taken only to exclude known gout. Of 1,024 determinations on 961 patients, only 59 or 5.7 per cent were over 6.4 mg. per 100 c.c. Those included 25 tests on patients with urea nitrogen retention, 16 with cardiac failure, eight malignant growths or leukemia, two pneumonia, four anemia or recent hemorrhage, and three, all below 6.8 mg., who subsequently had lower values and were considered normal. Only one patient, a diabetic, had a level of 9.1 mg. per 100 c.c., the only one of 961 individuals tested who might be considered to have constitutional hyperuricemia. This result was sufficient to discourage further attempts to discover the true incidence of constitutional hyperuricemia in the general population by this method.

Despite the obvious inadequacy of these data they were used tentatively as a basis for gene frequency analysis. Instead of using 1 in 1,000 for the proportion of hyperuricemia in the general population this figure was arbitrarily adjusted to 3 in 1,000 in order to be conservative in the conclusions. This assumption weights the argument strongly in favor of the theory that hyperuricemia is inherited as a recessive. Despite this advantage the theory earns little support in the following argument.

With hereditary characters the frequencies of homozygous dominants, heterozygotes, and homozygous recessives in a population mating at random agree with the equation  $d^2 + 2dr + r^2 = 1$ , where  $d$  (the frequency of the dominant gene) +  $r$  (the frequency of the recessive allele) = 1. If the incidence in the population is assumed to be 3 per 1,000, and the gene for the trait is dominant,  $d = 0.0017$ ,  $r = 0.9983$  and the corresponding frequencies

for  $d^2$ ,  $2dr$  and  $2r^2$  are 0.000 +, 0.003 — and 0.997 respectively. If the gene for the trait is recessive,  $d = 0.9453$  and  $r = 0.0547$  and genotypic frequencies are 0.894, 0.103 and 0.003 respectively. If hyperuricemia were a recessive, under these circumstances a gouty person would have one chance in 10 of choosing a mate who was heterozygous for the condition. As a recessive, gout could be transmitted by a gouty parent only if his spouse were heterozygous. Of 16 families of gouty fathers which produced sons (table 4) only three had affected sons indicating that the mothers were heterozygous. Since 12 of these families had only one son it seems likely that one or two other mothers also must have been heterozygous. Of six affected mothers, four had affected sons. It appears then that about 8 of 22 spouses would have been heterozygous. Of six affected mothers, four had affected sons. It appears then that about eight of 22 spouses would have been heterozygous, an incidence of about 1 in 3. The production of heterozygotes in one third of the population would require an incidence of homozygotes of about 3 per cent, a figure certainly much too high for hyperuricemia as we found it, and at great variance from the figure of 0.003 which was liberally assigned to it as a result of the survey of the general population.

In view of the fact that the most favorable interpretation possible of these very meager data leads to conclusions which in no way support the theory that hyperuricemia is a recessive trait, this supposition was abandoned. All of the phenomena observed seem to be adequately explained by assuming that hyperuricemia is inherited as a single autosomal dominant trait with incomplete penetrance.

The relationship between clinical gout and hyperuricemia is not completely clear. Hyperuricemia is inherited. It has been observed before puberty by Talbott.<sup>5</sup> There is reason to believe that the incidence of hyperuricemia in the population and the severity of hyperuricemia in the individual remain unchanged with advancing age. Gout, on the other hand is a disease of middle or late life, the incidence of which definitely increases as age advances.<sup>9, 10</sup> The occurrence of gout seems to be determined by environmental factors acting upon genetically susceptible people, those with hyperuricemia.

It is commonly thought by lay people that gout can be induced by over-indulgence and dietary indiscretions. Excessive intake of purine foods, malt liquors, and fats are known to cause an increase in the level of blood uric acid and to induce attacks of gout in susceptible individuals. Gout developed in G. H., secondary index, case No. 16, after this study was completed. Talbott<sup>5</sup> also has seen gout develop in people known to have hyperuricemia. Perhaps nothing will induce gout in non-susceptible individuals. Abnormally high levels of blood uric acid of themselves are not enough to guarantee attacks of gout. Patients with uremia, leukemia, polycythemia, pneumonia, malignancy, cardiac failure, and hemorrhage often develop hyperuricemia as high or higher than is seen in gout, without developing joint symptoms or tophi. Gout is dependent upon unknown factors in addi-

tion to high uric acid concentrates in the blood. These factors still remain unidentified despite intensive investigation for many years.

### SUMMARY

This study is based on 248 serum uric acid determinations on the 201 members of 44 gouty families as well as 1,024 serum uric acids on 961 patients examined routinely at City Hospital. A clear-cut division between hyperuricemia and normal was recognized clinically at 6.5 mg. per 100 c.c., which was confirmed by statistical analysis. The incidence of hyperuricemia in the relatives of gouty patients was found to be 18 per cent among 11 mothers, 17 per cent among 24 brothers, 21 per cent among 24 sisters and 15 per cent among 33 sons. Not a single daughter among 45 tested was found to have hyperuricemia.

There was no correlation between age and hyperuricemia among male relatives of gouty patients, but a significant correlation was found among female relatives. Since no female relative in this series was affected below the age of 50, it seems possible that normal menstrual function inhibits hyperuricemia.

On the assumption that gout and the hyperuricemia found in some of the relatives of gouty patients are the expression of the same genotype both in the same family and in different families, this series was developed in an attempt to detect the genetic mechanism involved. The genetic peculiarities of hyperuricemia are such that in some families it resembles an autosomal recessive, whereas in others it is more like an autosomal dominant. These peculiarities are, however, quite satisfactorily explained if the gene involved is an autosomal dominant which lacks penetrance in both sexes, but has a much lower penetrance in the female than in the male. A tentative estimate of the penetrance is about 84 per cent in the heterozygous male, about 12 per cent or less in the female. This conclusion brings the data of the pedigrees in good agreement with a tentative estimate of the gene frequencies in the general population.

*Note:* Since this article was submitted for publication, three studies have appeared which are pertinent to the subject: SMYTH, C. J., COTTERMAN, C. W., and FREYBERG, R. H., JR.: The genetics of gout and hyperuricemia—an analysis of 19 families, *Jr. Clin. Invest.*, 1948, xxvii, 749-759; SMYTH, C. J., STECHER, R. M., and WOLFSON, W. Q.: Genetic and endocrine determinants of the plasma urate level, *Science*, 1948, cviii, 514-515; HELLMAN, L.: Production of acute gouty arthritis by adrenocorticotropin, *Science*, 1949, cix, 280-281.

### BIBLIOGRAPHY

1. McCracken, J. P., OWEN, P. S., and PRATT, J. H.: Gout: still a forgotten disease, *Jr. Am. Med. Assoc.*, 1946, cxxxi, 367-372.
2. BROCHNER-MORTENSEN, K.: One hundred gouty patients, *Acta med. Scandinav.*, 1941, cvi, 81-107.
3. FOLIN, O., and DAVIS, W.: The diagnostic value of uric acid determinations in blood, *Arch. Int. Med.*, 1915, xvi, 33-37.

4. JACOBSON, D. M.: Uric acid in serum of gouty and non-gouty individuals; its determination by Folin's recent method and its significance in the diagnosis of gout, *Ann. Int. Med.*, 1938, xi, 1277-1295.
5. TALBOTT, J. H.: Serum urate in relatives of gouty patients, *Jr. Clin. Invest.*, 1940, xix, 645-648.
6. SMYTH, C. J., and FREYBERG, R. H.: A study of the hereditary nature of gout: a report of two families, *Ann. Int. Med.*, 1942, xvi, 46-56.
7. GARROD, A. B.: Observations on certain pathological conditions of the blood and urine in gout rheumatism and Bright's disease, *Med.-chir. Trans.*, London, 1848, xxxi, 83-97.
8. HOGBEN, LANCELOT: *Nature and nurture*, 1939, W. W. Norton Co., N. Y., p. 76.
9. WILLIAMSON, C. S.: Gout, *Jr. Am. Med Assoc.*, 1920, lxxiv, 1625-1629.
10. VORHAUS, M. G., and KRAMER, M. L.: Studies on thiamin chloride in gout, *Trans. Am. Therap. Soc.*, 1938, xxxviii, 109-115.

# THE USE OF CURARE (D-TUBOCURARINE IN OIL AND WAX) IN THE TREATMENT OF MUSCLE SPASM IN RHEUMATIC DISORDERS \*

By H. M. MARGOLIS, M.D., F.A.C.P., and PAUL S. CAPLAN, M.D.,  
*Pittsburgh, Pennsylvania*

THE present report records our preliminary observations in a consecutive series of 58 cases of various types of rheumatic disease in which treatment with curare in oil and wax was instituted. Curare was administered in 51 cases in which muscle spasm actually existed. The remaining seven cases were those in which a diagnosis of psychogenic rheumatism was made. In these, subjective symptoms of "muscle stiffness" without objectively demonstrable spasm were prominent along with many other bizarre musculoskeletal symptoms. Curare was used in this group primarily for control purposes, as an aid in evaluation of results in the larger group. Although the number of patients studied is not large, the results have been definitive. The conclusions to be drawn with regard to the effectiveness of the drug in the various syndromes studied are unmistakable. This preliminary report may indicate not only the area of usefulness of the drug, as revealed by our experience, but may encourage further interest in its study in other, related types of rheumatic disease.

The historical background of the use of curare, the pharmacologic properties of which were first demonstrated by Claude Bernard as far back as 1850, and its physiologic properties, as well as its more recent applications have been well described in a series of publications by Schlesinger and Ragan.<sup>1, 2, 3, 4, 5</sup>

Briefly, tubocurarine is a quarternary ammonium salt. These salts, as a group, possess the property of paralyzing conduction at the myoneural junction. In certain concentrations, tubocurarine has an almost pure myoneural junction effect. This neuromuscular block can be employed therapeutically, because with certain specific concentrations of curare as employed in the present study, involuntary muscle spasm is abolished, whereas voluntary muscular contraction is entirely unaffected.

The effect of curare in creating myoneural block has been known for many years. Practical application of this knowledge was not possible, however, until recently, when a crystalline derivative of the crude alkaloid, with predictable pharmacologic properties and toxicity became available. The earlier aqueous preparations of curare were not well suited to the treatment

\* Received for publication May 18, 1948.

From the Department of Medicine and the Arthritis Services of The Montefiore and St. Margaret Memorial Hospitals and The John C. Oliver Memorial Research Foundation of The St. Margaret Memorial Hospital.

of muscle spasm associated with syndromes of a chronic nature. Because of their rapid elimination their action was evanescent, and because of rapid absorption, aqueous preparations produced high concentrations of the drug, which may induce severe toxic side effects.

The preparation we have employed consists of a suspension of 3 per cent of d-tubocurarine chloride in 4.8 per cent wax and peanut oil. This suspension is given by intragluteal injection, yielding a slow acting effect, generally lasting from 24 to 48 hours, and in some instances more than 72 hours. With such dosage the desired clinical response may be elicited without serious reactions. Milder side effects, which will be described later, have occurred in some cases. As Schlesinger has shown in reports on his very extensive clinical experience with this drug, it is neither toxic, nor habit forming. Nor is there evidence that tolerance to the drug develops.<sup>3</sup>

When a suspension of d-tubocurarine chloride in wax and peanut oil became available<sup>1, 2, 3</sup> we became interested in the therapeutic value of this drug in the treatment of muscle spasm associated with a variety of rheumatic disorders. We realized, of course, that the basic pathologic process respon-

TABLE I

Diagnosis	Number of Cases	Definitely Beneficial	Not Beneficial	Questionably Beneficial
Rheumatoid arthritis	23	0	18	5
Periarthritis of shoulder	5	5	0	
Low back pain	13	7	4	2
Osteoarthritis with associated periarticular fibrositis	6	0	4	2
Fibromyositis	4	0	4	0
Psychogenic rheumatism	7	0	7	0

sible for the muscle spasm would require treatment. Nevertheless, we felt that resolution of the associated muscle spasm, if possible, might aid in functional rehabilitation at the earliest time. Protective splinting by muscle spasm may serve a useful purpose by preventing further irritation of the underlying pathologic lesion in the joint or bursa, but such spasm has its deleterious aspects. If a state of continuous spasm is allowed to persist muscles may undergo fixed contracture. Atrophy of the opposing extensor groups of muscles is likely to occur, and in certain inflammatory states such as rheumatoid arthritis, subacromial bursitis, and periarthritis of the shoulder, adhesive inflammatory changes may supervene with limitation of mobility requiring manipulative procedures for restoration of normal joint function.

The clinical evaluation of d-tubocurarine chloride in oil and wax suspension is based on study of cases in the following categories: (1) rheumatoid arthritis, (2) periarthritis of the shoulder, (3) low back pain, (4) osteoarthritis with associated periarticular fibrositis, (5) fibromyositis, (6) psychogenic rheumatism (table 1).

The results were recorded as either definitely beneficial; not beneficial; questionably beneficial.

Results were tabulated as definitely beneficial only when striking relief of symptoms occurred with curarization (estimated at an average of 85 per cent). These findings were confirmed by objective examination.

Results were tabulated as questionable when the patient reported slight subjective improvement which could not be confirmed by objective examination. In many instances it was felt that subjective change could not be directly attributed to curarization.

### ANALYSIS OF RESULTS

*Rheumatoid Arthritis.* There were 23 cases of generalized rheumatoid arthritis. The duration of the disease varied from one to 20 years, the majority of the patients (16 cases) having been ill for over five years. All presented typical clinical and roentgenographic evidence of rheumatoid arthritis; all were in a stage of activity as indicated clinically and by rapid sedimentation rates, and many of them showed characteristic deformities. These patients received three to six injections of 175 units (1.0 c.c.) of curare in wax and peanut oil every two to three days; this treatment was continued with one patient for a period of six weeks. In several instances reactions without relief of muscle spasm were noted following injection. In these cases administration of the drug was discontinued.

In none of these patients was there clinical evidence of definite improvement, either subjective or objective. In five cases there was questionable subjective improvement which could not be confirmed by examination. It is perhaps significant that of these five, one was suffering from Marie-Strumpell (rheumatoid) spondylitis and four presented evidence of Marie-Strumpell spondylitis associated with rheumatoid arthritis of peripheral joints. Three cases of typical rheumatoid spondylitis, however, were not benefited either subjectively or objectively.

*Periarthritis of Shoulder.* There were five cases of periarthritis of the shoulder. The roentgenograms in all were normal.

These patients presented the characteristic symptoms of pain in the shoulder and along the course of the deltoid muscle, pain always increased by attempts at abduction, external or internal rotation of the arm. In all cases normal range of motion was to some degree restricted. Definite adhesive changes limiting the range of mobility were associated in two. In these, manipulation of the shoulder under anesthesia was performed. In the other three cases restriction in the range of motion was caused entirely by muscle spasm. In one of these, manipulation of the shoulder was performed in the course of tonsillectomy, but no adhesions were present.

In all five cases of periarthritis of the shoulder there was distinct improvement, both subjectively and objectively, attributable to the administration of curare. In the two cases in which manipulation was performed to break



up adhesions, subsequent administration of curare along with the usual physiotherapeutic measures was of definite benefit in relieving muscle spasm and thus increasing the range of motion.

These patients were generally given 1.0 c.c. of curare every other day during the stage of most severe muscle spasm. Following improvement 1.0 c.c. was given weekly during the course of follow-up treatment until the normal range of motion was restored. These patients all received, in addition, physiotherapy, including infra-red heat, massage, and active exercises with or without assistance, depending upon the need or capacity of the patient. The results immediately following each injection of curare were so striking, however, that there can be no question of the effect of the drug in this condition. With relief of muscle spasm, less analgesia was required and active exercises were carried out more easily, less painfully. The result was acceleration in the restoration of the normal range of joint function.

*Low Back Pain.* There were 13 patients with low back pain resulting from varying causes. In seven of these cases, prompt and striking objective and subjective improvement followed the administration of curare; in four, the drug had no effect; in two, improvement following curare was questionable.

Of the 13 patients in this group, two with acute traumatic low back sprain were completely relieved of muscle spasm and of subjective symptoms by a single injection of 1.0 c.c. of curare in oil and wax. In one, roentgenograms of the lower back were negative; in the other, the acute sprain was superimposed upon a chronic, degenerated lumbar intervertebral disc. A third case of acute traumatic sprain evidenced no effect from curare. The sprain was superimposed upon osteoarthritis of the lumbar spine in a gouty patient who had also been suffering for some time from a rather severe anxiety state.

In five patients with acute low back pain *without* sciatic radiation, related to osteoarthritis of the lumbar spine, four obtained prompt, marked relief after the first injection of curare, with practically complete abeyance of distress and marked subsidence of muscle spasm. In the fifth patient, no beneficial effect was observed. The degree of osteoarthritis and the duration of symptoms in the latter case did not differ significantly from that in the other four. Perhaps the fact that this patient was attempting to secure workman's compensation contributed to difficulty in evaluating the effect of curare.

Of the four patients with advanced osteoarthritis of the lumbar spine *with* sciatic radiation of pain, only one definitely benefited from curare. In this case, the sciatica was of reflex origin, unrelated to direct nerve root irritation or pressure. In two patients in whom no improvement occurred, there was evidence of direct sciatic nerve root irritation or pressure. It is significant that in these two cases, back pain and lumbar muscle spasm may have been somewhat ameliorated with curare, but the sciatica was aggravated. In the fourth case the effect of curare was questionable.

In a patient with postural low back strain with lumbar muscle spasm the effect of curare was also only questionable.

*Osteoarthritis with Associated Periarticular (Capsular) Fibrositis.* Six patients with clinical and roentgenographic evidence of osteoarthritis of peripheral joints with associated periarticular (capsular) fibrositis of either degenerative or perhaps infectious origin were treated.

In two of these patients questionable subjective improvement resulted from the administration of curare. Both were elderly. In both the onset of the fibrositic symptoms followed an acute respiratory infection; the sedimentation rates were accelerated. The findings indicated a capsulitis of apparently infectious origin, superimposed upon marked generalized osteoarthritis. Although these patients reported some alleviation of morning stiffness, the effect was negligible and probably attributable to the general therapeutic measures; rest, analgesics, and physiotherapy used concomitantly with curare.

Four of these patients presented osteoarthritis of the peripheral joints with symptoms indicative of an associated capsulitis of degenerative origin. They all had normal sedimentation rates. In none of these was there evidence of improvement, either objective or subjective, after repeated administration of curare in oil and wax.

*Fibromyositis.* Four patients with fibromyositis failed to derive any benefit from repeated administration of curare. One of these patients suffered from a generalized fibromyositis following an acute upper respiratory infection. The second patient manifested characteristic fibromyositic symptoms involving the shoulders, hips, and lower back. The fibromyositis in the third and fourth patients was localized to the cervical region.

*Psychogenic Rheumatism.* Seven patients presented the typical syndrome of psychogenic rheumatism in which a feeling of stiffness, muscle aching, and other types of pain, often bizarre, were associated with other psychoneurotic personality traits. A diagnosis of psychogenic rheumatism had previously been established both by direct examination as well as by exclusion of organic musculoskeletal disease. There was no hope of obtaining any therapeutic benefit in this group; they served as a control. In none of these cases was any improvement noted. Two patients described some degree of subjective improvement, but this, however, did not correspond to the usual description of the effect of curare. Subsequent injections of curare were said to have been of no benefit or to have been followed by actual increased severity of symptoms.

## DISCUSSION OF RESULTS

The beneficial effects of curare are always evidenced by prompt, dramatic relief of muscle spasm, generally after the first injection of the drug. Hence, long periods of trial are unnecessary. The specific physiologic effect of the drug is so clear cut that when beneficial therapeutic results are forthcoming, they should be evident to some degree after the very first injection. Except in the case of patients with psychogenic rheumatism, the response is generally

repetitive, equally effectively elicited by subsequent injections. The patient with psychogenic rheumatism may describe subjective benefit after the initial injection of curare; but he is susceptible to the influence of suggestion by "an injection" of any type. He may report "much relief" or "improvement" following the initial injection of curare. More detailed questioning with regard to the effect will elicit a quite atypical description. Moreover, subsequent injections of curare in such cases are likely to produce "little" or "no beneficial" effect, or even "more muscle stiffness." Such experiences serve as striking controls for those cases of organic rheumatic states with evidence of muscle spasm, in whom the description of subjective relief generally follows a distinctive pattern. In such cases subjective improvement can be correlated with and confirmed by physical examination which indicates resolution of muscle spasm.

As can be noted in table 1, our results in treatment of muscle spasm in the group of patients with rheumatoid arthritis has been entirely discouraging. Occasionally, subjective relief of muscle spasm was reported, as for example in one case with relief of adductor spasm associated with rheumatoid arthritis of the hips. We were not surprised at the ineffectiveness of curare in the alleviation of muscle spasm in rheumatoid arthritis, especially cases of advanced degree, such as we have treated thus far. It must be remembered that the muscle spasm of rheumatoid arthritis is probably caused not only reflexly by the local joint inflammation, but probably also by infiltration of the muscle mass with an inflammatory exudate, as has been demonstrated by Freund and his associates,<sup>6</sup> and as we have found in many muscle biopsies in rheumatoid arthritis. In rheumatoid arthritis there is, moreover, an inflammatory capsulitis with a certain degree of spasm or contracture of the joint capsule.

We have not had the opportunity of administering curare to patients in the earliest phases of rheumatoid arthritis. It is possible that the drug might prove to be of value in such early cases, before muscle spasm has been seriously complicated by the element of muscular and capsular contracture, and the effect of the inflammatory exudate in the muscle itself. Schlesinger and Ragan,<sup>4</sup> whose experience with curare in rheumatoid arthritis was more favorable than ours, employed the drug in the *acute* phase of the disease: one of the two cases cited by them having had an acute onset of rheumatoid arthritis two months before admission; the other six months before. It would appear from these and our less encouraging results in more advanced cases, that the effectiveness of curare in rheumatoid arthritis will, if at all evident, probably be limited to the earliest phases of the disease.

In the treatment of periartthritis of the shoulder the effectiveness of curare is especially striking. It is most obvious when adhesive changes do not exist and the limitation of movement and pain is caused entirely by muscle spasm. Obviously, curare will not resolve adhesions within the subacromial bursa or between the capsule of the shoulder. But even in adhesive bursitis or capsulitis of the shoulder, curare may be valuable if em-

ployed in conjunction with physiotherapy and manipulative exercises. By overcoming muscle spasm, it may be possible in some of these instances to restore the full range of motion in the shoulder by physiotherapeutic measures, including exercise, when manipulative therapy under anesthesia might otherwise be required. The use of curare is also strikingly beneficial in conjunction with physiotherapeutic measures which we institute promptly after the breaking up of adhesions under anesthesia. In such cases we have found that the therapeutic exercises following manipulation were carried out more easily, with less discomfort, and with a better ultimate result, attained in a much shorter period of time. The number of cases so treated is small, however, so that final evaluation is not possible at this time.

The beneficial results of curare in the relief of low back pain demonstrates the specific value of this drug in the abolition of reflex muscle spasm. Curare should find its greatest field of usefulness in the treatment of low back pain when there is muscle spasm of reflex origin. Our two patients with low back pain (without sciatic radiation) who were not benefited from curare presented associated factors, especially an unfavorable psychogenic component which militated against a favorable result. Their evidence should therefore not detract from the otherwise consistently favorable results in this group of cases.

We found curare to be of no value in low back pain with sciatic radiation caused by nerve root irritation or pressure. These results confirm the observations of Schlesinger and Ragan<sup>4</sup> who also noted that with removal of the splinting action of muscle spasm, sciatic pain resulting from direct nerve root involvement was increased.

Relief of muscle spasm and pain which the use of curare affords in the treatment of periarthritides of the shoulder and low back pain is dramatic. It would be unsound, of course, to discard other proved therapeutic measures specifically applicable to the underlying pathologic lesion. The contribution of curare is the abolishment of the cycle of muscle spasm and pain which often constitutes a most trying and protracted problem. Earlier rehabilitation of the patient is then possible.

In the treatment of osteoarthritis of peripheral joints with associated degenerative periarticular (capsular) fibrositis, curare is generally unsatisfactory. Since the restriction of mobility and pain in these cases is related largely to changes in the joint cartilage and articular capsule and not primarily to reflex muscle spasm, the absence of a favorable response to therapy with curare is not surprising.

Curare has also proved totally ineffective in the syndrome of fibromyositis.

The lack of benefit to be derived from the use of curare in cases of psychogenic rheumatism merely serves to define more sharply the specific problems in which it may be helpful.

Reactions followed the administration of curare in 12 of the 58 patients. For the most part reactions were mild and not disabling, and consisted of

blurring of vision, vertigo, and weakness. Blurring of vision was the earliest manifestation; vertigo, generalized weakness and numbness developed if the reaction was more severe. In two cases the muscular weakness was severe enough to incapacitate the patient completely for several hours. Because of the possibility of such a reaction, curare should not be given to ambulatory patients unless they can reach their homes very shortly after an injection.

Prostigmine methylsulfate intramuscularly or intravenously or prostigmine bromide by mouth may be given to overcome the more severe reactions.

An important precaution is the use of a perfectly dry syringe and needle to prevent formation of water soluble and rapidly absorbed curare which may be responsible for unusually severe reactions.

### SUMMARY AND CONCLUSIONS

1. This report deals with our clinical observations with a slowly acting suspension of d-tubocurarine in wax and peanut oil in the treatment of 58 cases of various types of rheumatic disease, including rheumatoid arthritis. The results justify rather definitive conclusions with regard to the therapeutic effectiveness of curare in the alleviation of reflex muscle spasm only in certain specific rheumatic disorders and its ineffectiveness in certain other types of rheumatic disease.

2. D-tubocurarine in oil and wax has served to relieve the muscle spasm, and indirectly the limitation of motion and pain, in non-adhesive peri arthritis of the shoulder. It has facilitated the physiotherapeutic management and recovery and shortened the period of treatment in adhesive peri arthritis of the shoulder when manipulation under anesthesia was necessary for breaking up of adhesions.

3. Curare was found to be especially useful in the treatment of low back conditions associated with muscle spasm. Curare affords the most striking relief of symptoms by abolishing muscle spasm in hypertrophic arthritis of the spine and in acute low back sprain, permitting earliest rehabilitation of the patient.

4. Curare was of no benefit in patients with low back syndrome with sciatic pain resulting from direct nerve root irritation or pressure.

5. D-tubocurarine in oil and wax has been practically without effect in the alleviation of the muscle spasm associated with advanced rheumatoid arthritis.

6. In our experience curare has not been effective in relieving the muscle spasm and "stiffness" which occurs in osteoarthritis of peripheral joints with associated periarticular fibrositis. It was totally ineffective in relieving the "stiffness" of primary fibromyositis.

7. As might be expected, curare was also totally ineffective for relief of "muscle stiffness" of psychogenic rheumatism.

8. Reactions from the drug sometimes occur. They are generally mild, but may in some instances cause diplopia, vertigo, and severe muscle weak-

ness. Prostigmine, an antagonist to curare, may be employed to overcome the more severe reactions.

#### BIBLIOGRAPHY

1. SCHLESINGER, E. B.: The use of suspension of tubocurarine in oil in the treatment of spasticity, *Arch. Neurol. and Psychiat.*, 1946, lv, 530.
2. SCHLESINGER, E. B.: Recent advances in the use of curare in clinical practice, *Bull. N. Y. Acad. Med.*, 1946, xxii, 520.
3. SCHLESINGER, E. B.: Curare: a review of the therapeutic effects and their physiological basis, *Am. Jr. Med.*, 1946, i, 518.
4. SCHLESINGER, E. B., and RAGAN, C.: "Muscle spasm" in acute low back pain and similar syndromes, *Am. Jr. Med.*, 1946, i, 621.
5. SCHLESINGER, E. B.: Therapeutic applications of curare and their physiologic implications, *N. Y. State Jr. Med.*, 1947, xlvii, 1689.
6. STEINER, G., FREUND, H. A., LICHENTRITT, B., and MAUN, M. E.: Lesions of skeletal muscles in rheumatoid arthritis. Nodular polymyositis, *Am. Jr. Path.*, 1946, xxii, 103.

# AN EVALUATION OF RADICAL SURGERY FOR CARCINOMA OF THE PANCREAS AND AMPULLARY REGION\*

By ALLEN O. WHIPPLE, M.D., *New York, N. Y.*

THE justification for present day radical surgery should be determined by the threat of the untreated lesion, the operative risk if radically treated, the life expectancy after operation, and the prospect of comfortable living subsequently. Radical surgery may be curative, but much of it may be only palliative. This of course is true of many forms of medical therapy.

Radical surgery of the past 15 years, and especially that of today, has been made possible by many factors: a better understanding of supportive treatment, blood transfusion, maintenance of fluid, protein and electrolyte balance, improved methods of anesthesia, intelligent use of chemotherapeutic agents. But above all, a newer generation of physiologically minded and trained surgeons, especially the resident trained surgeons, more interested in an understanding of the needs of the sick, debilitated patient and in restoring his physiological balance, than in the speed of the operation or in showmanship.

The very few earlier attempts, in the first two decades of the century, to resect ampullary growths and the head of the pancreas with a portion of the duodenum proved so hazardous that they were abandoned.<sup>1</sup> In the early thirties, successful removal of islet cell tumors had demonstrated that the pancreas was not an untouchable organ.<sup>2</sup> In 1934, when the attempts to remove carcinomatous growths from the ampullary area were renewed at the surgical clinic of the Columbia-Presbyterian Medical Center,<sup>3</sup> the risk of persistent bleeding in the deeply jaundiced patient required a two stage procedure. But it was demonstrated that the head of the pancreas, with all of the duodenum, the antrum of the stomach, the lower end of the common duct, and the retroduodenal gland-bearing area could be resected.

By 1940, vitamin K therapy had been introduced and by its use the bleeding tendency could be controlled. In March of that year, we<sup>4</sup> carried out the first one stage resection of the above structures in a woman with a carcinoma of islet tissue in the head of the pancreas. This patient is still alive and active.

Since then, many modifications of the one and two stage radical procedures have been successfully carried out, some 220 of them in five of the clinics of this country (table 1). Reports of these procedures are now beginning to come from foreign clinics. Furthermore, since Priestley's<sup>5</sup> first total pancreatectomy for hyperinsulinism in 1944 (this patient is alive and

\*Read before the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 31, 1949.

well, requiring only 20 to 30 units of insulin per day) some 20 others have been reported.

In these radical procedures, the operative risk, the long term followup, and the comfortable physiology and relief from pain and jaundice depend upon several factors: (1) the type of the carcinoma, (2) the site of the tumor, (3) the early diagnosis of the lesion, before it has spread to the lymph nodes and peritoneum, (4) the radical, en bloc, removal of the growth with part or all of the pancreas, the entire duodenum, the lower end of the common duct, the antrum of the stomach, and the retroduodenal and pancreatic lymph nodes.

### THE TYPE OF CARCINOMA

Carcinoma of the papilla of Vater and the ampullary area is usually a fungating adenocarcinoma, growing into the lumen of the duodenum with a slower invasion of the lymphatics. Carcinomas of the pancreas are more often of the invasive, infiltrating, undifferentiated type, spreading rapidly into the lymph nodes and metastasizing to the liver and peritoneum.

### THE SITE OF THE TUMOR

Ampullary growths obstruct the bile and pancreatic ducts more quickly and completely than those in the pancreas, and give the important warning signal of jaundice earlier. Courvoisier's syndrome of painless jaundice with an enlarged gall bladder is most frequently seen in the patients with ampullary tumors. However, not all of these patients are pain-free, yet the pain is not as severe, constant, or radiating to the back as it is in pancreatic carcinomas of the body or tail.

In carcinoma of the pancreas, the warning signal of jaundice depends upon the proximity of the growth to the common duct. It is usually absent in carcinoma of the body and tail. Pain, as mentioned, is usually more severe and constant, worse on lying down and frequently of a boring character, radiating into the back. The more distant from the ampulla, the later the diagnosis as a rule, and the worse the prognosis.

### EARLY DIAGNOSIS

Aside from the essential history and physical examination, which in many patients establishes the early diagnosis, certain laboratory procedures are helpful and must be emphasized. The most important is the study of the duodenal contents. This is based upon the early sound observations of Pavlov,<sup>6</sup> who demonstrated the effect of increased pancreatic external secretion by vagal stimulation, and of Bayliss and Starling,<sup>7</sup> who demonstrated the hormonal action of secretin in accelerating the flow of pancreatic juice. Since then, Lagerlöf<sup>8</sup> in Stockholm, Comfort<sup>9</sup> and his associates at the Mayo Clinic, and Bauman<sup>10</sup> at the Columbia-Presbyterian Clinic in this country have demonstrated the value of duodenal intubation in the differen-



tial diagnosis of jaundice and of ampullary and pancreatic lesions. In aspirating the fasting duodenal contents by the double tube Lagerlöf technic, the important findings are the amount of bile and presence or absence in it of cholesterol crystals and bile pigment particles, the amount or absence of pancreatic juice, the presence of red blood cells, the presence of tumor cells.

Marked diminution or absence of bile and pancreatic juice, with the presence of red blood cells or tumor cells, indicates a carcinoma of the papilla. Normal amount of pancreatic juice with marked diminution or absence of bile plus red blood cells points to a carcinoma of the common duct. Normal bile but diminished or absent pancreatic juice plus red blood cells implies a carcinoma of the pancreas. Cholesterol crystals or bile pigment particles indicate the presence of gall stones. The finding of tumor cells in the centrifuged specimens establishes the diagnosis of neoplastic disease. Ampullary carcinoma was diagnosed last November at the Memorial Hospital by the finding of tumor cells, and proved by a radical pancreatoduodenectomy. Jaundice with an elevated serum phosphatase means obstruction of the common duct. Absence of jaundice does not rule out a growth in the pancreas.

Careful barium roentgen-ray studies of the duodenum may show a filling defect by a fungating growth of the ampulla or a distortion or increase in the C-curve of the duodenum, the result of a tumor in the head of the pancreas.

The only hope of permanent results with radical surgery in these cancers is the early diagnosis of localized lesions. In the majority of cases, the general practitioner and the internist are first consulted, and are responsible for prompt and early diagnosis, or a fatal delay by studying the patient until the diagnosis is obvious and the lesion inoperable. The internist is as important as the surgeon in the cure of these patients.

## RESULTS

The average life expectancy in carcinoma of the pancreas treated expectantly is about six months. A palliative bile shunting operation, preferably a cholecystojejunostomy, relieves the patient of intolerable pruritus and temporarily improves digestion, and should be done if the growth is found inoperable.

During the first 10 years of this radical surgery, the operative mortality was high in the 30 per cent level. But with the improvements in pre- and postoperative therapy and in the operative technic, this hazard has been markedly reduced. Cattell<sup>11</sup> has the remarkable record of a 13.6 per cent mortality in 59 patients. He has carried out pancreatoduodenectomy in 22 patients with ampullary growths, with only one death.

Drs. Parsons and Lockwood<sup>12</sup> have not lost a patient in their last 13 radical procedures. Dr. Waugh<sup>13</sup> of the Mayo Clinic has lost only one patient in the last 15 pancreatoduodenectomies.

The radical surgery for ampullary carcinoma gives better results than for carcinoma of the pancreas itself. From the five clinics mentioned, eight

patients lived five years or more, after removal of ampullary growths—two of them over seven years. Of the collected cases of carcinoma of the pancreas, three have survived five years or more,—two of them operated upon by Brunschwig.<sup>14</sup> One of these, the first one stage radical resection for carcinoma of islet cells, is living over nine years, but may have liver metastases at present. This is not a functioning islet cell tumor, however. In Cattell's<sup>11</sup> largest series of 59 patients operated upon for carcinoma, 30 per cent lived three years or more.

The fact that it has been demonstrated that cancer cells can be readily found in pancreatic duct fluid in cases of pancreatic carcinoma, and that trypsin favors the transplantation of cancer cells in experimental animals<sup>15</sup> would explain the high incidence of recurrence in resection of the pancreas, and may be a definite indication for a total pancreatectomy in patients with carcinoma of the pancreas.

#### BIBLIOGRAPHY

- KAUSCH, W.: Das Carcinom der Papilla duodeni und seine radikale Entfernung, *Beitr. klin. Chir.*, 1912, lxxviii, 439-486.
- HIRSCHEL, G.: Die Resektion der Duodenums mit der Papille wegen Karzinoms, *München. med. Wchnschr.*, 1914, lxi, 1728.
- TENANI, O.: Contributo alla chirurgia della papilla del Vater, *Policlinico*, 1922, xxix, 291.
- HOWLAND, G., CAMPBELL, W. R., MALTBY, E. J., and ROBINSON, W. L.: Dysinsulinism; convulsions and coma due to islet cell tumor of pancreas, with operation and cure, *Jr. Am. Med. Assoc.*, 1929, xciii, 674-679.
- WHIPPLE, A. O., PARSONS, W. B., and MULLINS, C. R.: Treatment of carcinoma of the ampulla of Vater, *Ann. Surg.*, 1935, cii, 763.
- WHIPPLE, A. O.: Pancreatoduodenectomy for islet cell carcinoma: a five year followup, *Ann. Surg.*, 1945, cxxi, 847.
- PRIESTLEY, J. T., COMFORT, M. W., and RADCLIFFE, J.: Total pancreatectomy for hyperinsulinism, *Ann. Surg.*, 1944, cxix, 211.
- PAVLOV, J. P.: Die Arbeit der Verdauungsdrüsen, 1898, Wiesbaden.
- BAYLISS, W. M., and STARLING, E. H.: The mechanism of pancreatic secretion, *Jr. Physiol.*, 1902, xxviii, 325.
- LAGERLÖF, H. O.: Pancreatic function and pancreatic disease studied by means of secretin, 1942, P. A. Norstedt and Söner, Stockholm.
- COMFORT, M. W., PARKER, R. L., and OSTERBURG, A. E.: Concentration of pancreatic enzymes in the duodenum of normal persons and persons with disease of the upper abdomen, *Am. Jr. Digest. Dis.*, 1939, vi, 249.
- BAUMAN, L., and WHIPPLE, A. O.: The diagnostic value of pancreatic function tests in 47 surgically treated patients, *Am. Jr. Med. Sci.*, 1944, ccvii, 281.
- CATTELL, R. B., and PYRTEK, L. J.: An appraisal of pancreatoduodenectomy: a followup study of 61 cases. Read before the Southern Surgical Association Meeting, Dec. 6, 1948; to be published in *Ann. Surg.*, 1949. Also personal communication, March 8, 1949.
- LOCKWOOD, J. S.: Personal communication, March 28, 1949.
- WAUGH, J. M.: Personal communication, March 15, 1949.
- BRUNSCHWIG, A.: Personal communication, March 20, 1949.
- HOWES, E. L.: Experiments not yet published. Quoted by Dr. Lockwood.

# THE USE OF MIXTURES OF PROTAMINE ZINC AND REGULAR INSULIN \*

By RANDALL G. SPRAGUE, M.D., F.A.C.P., *Rochester, Minnesota*

DURING the past 10 years a considerable experience in the use of adjustable mixtures of protamine zinc and regular insulin in the Section on Metabolism Therapy of the Mayo Clinic has led to the formation of certain opinions about the usefulness and limitations of this method of insulin therapy of diabetes. Among other things, it has become apparent that appropriate mixtures, because of the intermediate character of their action with respect to onset, intensity and duration, have great usefulness in cases of moderately severe to severe diabetes. It is in these cases that protamine zinc insulin, used alone, lacks sufficient intensity of action to prevent undesirable degrees of postprandial hyperglycemia and glycosuria while still retaining a capacity for causing serious hypoglycemia during the fasting hours of the night.

It is my purpose in this paper to describe the background for our present opinions about the use of mixtures of protamine zinc and regular insulin, and by way of illustrating the place of mixtures in the therapeutic scheme, to analyze the types of insulin therapy employed in 246 patients with diabetes seen late in 1948 and early in 1949.

This group of patients, as well as the diabetic practice of the clinic in general, requires description, for the character of the practice has some bearing on the interpretation of results. Approximately half of all the diabetic patients seen in the clinic each year are treated as ambulatory patients. Most of these take their meals, according to individually prescribed diet formulas, in the Rochester Diet Kitchen.† All of the patients to be described herewith were ambulatory outpatients throughout the period of their treatment and instruction. Hospital patients were excluded from consideration because of the common presence in them of complicating medical or surgical conditions which make the results of therapy of diabetes more difficult to evaluate. The group to be described probably included more than the usual proportion of "difficult" conditions, from the standpoint of diabetic management, because many of these patients were referred to the clinic for advice when major problems in their management were encountered at home. The

\* Read at the Thirtieth Annual Session of The American College of Physicians, New York, N. Y., March 31, 1949.

† The diet kitchen provides a means whereby fairly rigid dietary control of diabetes can be maintained while the patients are ambulant and receiving instruction in the management of their disease. All servings of food are weighed or carefully estimated according to the requirements of the individual patient. Experience has shown that the patients learn more quickly and more satisfactorily when ambulant outpatients than they do in the hospital. From day to day they are permitted to assume increasing responsibility in their own care.<sup>1</sup> By exchanging notes and experiences with other ambulant patients, and having regular conferences with physician and dietitian, the learning process is accelerated.

period of observation of these patients was often shorter than desirable, so that in many instances the daily dose of insulin was considerably more at the time of dismissal than it subsequently became at home, and the control of glycosuria in some instances was not the best attainable.

The fact that the response of diabetic patients to treatment differs is frequently overlooked. That such variability actually exists is illustrated by the well-known fact that in almost half of all cases of diabetes the disease is well controlled by diet therapy alone, while in the other half insulin in addition to diet is necessary. Furthermore, among patients who require insulin there is a great variability in response to treatment. The reasons for this variability are not well understood. It may perhaps indicate that there are different forms of the disease, different etiologic factors, or possibly only differences in the intensity of the disease. In any event, it is important to be aware of the inherent ease or difficulty of therapy in different diabetic patients before a program of administration of insulin is chosen in any given case, and before the merits of any particular system of therapy employed in a group of cases are judged.

Stated simply, in some diabetic patients the disease is easily controlled by almost any program of administration of insulin, whereas in others the timing characteristic of the action of the insulin employed must be carefully tailored to the needs of the individual. In the latter group of cases a relatively intense insulin action usually is needed during the day when food is being ingested, and a relatively feeble insulin action, during the fasting hours of the night. Insulin therapy to be effective in cases of severe diabetes must be arranged so that account is taken of the fact that the human subject eats during the day and fasts during the night. Furthermore, there is a small group of patients—those who have so-called unstable or brittle diabetes—in whom it is virtually impossible to maintain sugar-free urine and freedom from insulin reactions with any type or combination of insulins now available. In this group it seems that nothing short of an “automatic” insulin, with rate of absorption determined by the level of the blood sugar, would accomplish precise control. Unfortunately, there is at present no indication that an insulin with such a high order of intellect will ever be developed.

#### DEVELOPMENT OF THE USE OF MIXTURES OF INSULIN

In this country Colwell,<sup>2</sup> MacBryde,<sup>3</sup> Peck<sup>4</sup> and others have made intensive studies of the action of mixtures of regular and protamine zinc insulin in diabetic patients. Colwell,<sup>2</sup> in particular, in a series of excellent papers published since 1942, has described with considerable precision the timing characteristics of mixtures of varying proportions of regular and protamine zinc insulin. Briefly, it has been shown that it is necessary to mix at least one part of regular with one part of protamine zinc insulin to secure definite modification of the action of the latter. Intensification and shortening of action is not sufficiently marked to be therapeutically useful

until a ratio of 2 units of regular to 1 unit of protamine zinc is reached. With additional increases in the proportion of regular insulin, the action of the mixture is further intensified and shortened. The obvious implication is that appropriate mixtures should be superior to protamine zinc insulin from the standpoint of control of postprandial glycosuria during the day and prevention of hypoglycemic reactions at night in the patient with severe diabetes.

In contrast to the experimental studies of Colwell, our own acquaintance with the action of mixtures has been based almost exclusively on their clinical use. Shortly after Lawrence,<sup>5</sup> in 1938, published a brief description of the treatment of diabetes with mixtures, we in the Section on Metabolism Therapy at the Mayo Clinic began to treat certain types of diabetic patients with mixtures and have been doing so ever since.

The development of our knowledge of the action of mixtures, on the basis of clinical observation, makes an interesting story. Initially, in 1938, we started to combine in one syringe the doses of regular and protamine zinc insulin which we had previously been giving in separate sites. Consequently the early mixtures consisted of relatively small amounts of regular insulin and relatively large amounts of protamine zinc insulin. Thus, it was not uncommon for the patient with severe diabetes to receive a mixture consisting of, say, 40 units of protamine zinc and 10 units of regular insulin. With close observation of numerous patients, it became apparent before long that the action of such mixtures closely resembled that of protamine zinc insulin alone. In patients with severe diabetes, insulin reactions tended to occur between midnight and the time for rising, and excessive glycosuria during the day was almost the rule. In other words, the use of such mixtures offered no particular advantage, for the difficulties for which regular insulin was added to protamine zinc insulin remained uncorrected.

Eventually we added more regular insulin to the mixtures, in an effort to reduce glycosuria during the day and decreased the amount and proportion of protamine zinc insulin in an effort to prevent the insulin reactions which our patients were experiencing too frequently in the early morning hours. Before long we were finding that the great majority of patients with diabetes of sufficient severity to require the use of mixtures were being treated with mixtures containing as much, or more, regular insulin as protamine zinc insulin. By 1940 or 1941 it had become apparent that in most cases in which mixtures were employed, the ratio of regular to protamine zinc insulin lay between 2 : 1 and 3 : 1.

At the same time it became obvious, as had been anticipated, that the mixtures which contained higher proportions of regular insulin actually did provide better control of daytime glycosuria and did lessen the hazard of nocturnal insulin reactions in patients with severe diabetes who had formerly been treated with protamine zinc insulin alone. Thus, by a fairly prolonged process of clinical trial and error, we arrived at an appreciation of the timing of the action of mixtures which coincided in all essential respects with Col-

well's descriptions of their action, arrived at by rigidly conducted experimentation.

One further digression is necessary before proceeding to a consideration of the treatment employed in our recent group of cases. This concerns the vexing questions of what constitutes control of diabetes and, once control has been defined, how important is it? Is it necessary to set one's therapeutic goal any higher than the simple avoidance of ketosis and severe insulin reactions? These questions have not yet been answered satisfactorily, and he who pretends to know the answer is basing his opinion more on feeling than on actual knowledge. I am personally of the opinion that control (or lack of it) is probably not the only, or even the crucial factor in the prevention (or development) of the so-called degenerative complications of diabetes, arteriosclerosis, retinopathy, neuropathy and intercapillary glomerulosclerosis, which are being observed with increasing frequency among diabetic patients who have been kept alive for many years by use of insulin. Nevertheless, as Ricketts<sup>6</sup> has pointed out, the burden of proof is on the one who says that control is unimportant. Prolonged periods of unbridled glycosuria, perhaps associated at times with mild ketosis, might well be one factor in the development of degenerative complications, even if not the sole factor. Therefore, until the contrary is proved, we should continue to strive for as precise control of glycosuria as is possible and compatible with a reasonably simple program of treatment and the avoidance of insulin reactions.

#### TYPES OF INSULIN THERAPY RECENTLY EMPLOYED

Now to proceed to a consideration of the types of therapy employed in the recent group of 246 ambulatory diabetic patients. This particular number of patients was chosen for study because it included exactly 100 patients who were treated with extemporaneous mixtures of regular and protamine zinc insulin. These 100 patients will be subjected to closer scrutiny than the rest because it is treatment with such mixtures that interests us at this time.

First, it will be noted that of the total of 246 patients, 96 (or 39 per cent) required only diet therapy, without the use of insulin, for control of glycosuria (table 1). We have made a practice of omitting insulin only in those cases in which the urine is demonstrated to remain consistently free of sugar while the patient is on an adequate diet without the use of insulin. This figure is somewhat lower than that for the total diabetic practice of the clinic,

TABLE I  
Therapy Employed Recently in 246 Cases  
of Diabetes Mellitus (1948-1949)

Therapy	Cases	Per cent
No insulin	96	39
Insulin	150.	61

probably because a large number of patients with mild diabetes are excluded who were not treated as ambulant patients or who were seen in the hospitals for reasons unrelated to the presence of diabetes. Among the 150 patients who were treated with insulin two of every three were taking mixtures at the time of their dismissal from our care (table 2).

TABLE II  
Insulin Therapy Employed Recently in 150 Cases  
of Diabetes Mellitus (1948-1949)

Insulin	Cases	Per cent
Protamine zinc	36	24
Regular only	0	0
Mixed regular and protamine zinc	84	56
Mixed regular and protamine zinc plus supplementary doses of regular	16	11
NPH 50	5	3
Globin only	9	6
Total	150	100

The percentage of patients who were treated with a single dose of protamine zinc insulin taken in the morning before breakfast is relatively small (36 cases or 24 per cent of those for whom insulin was used), probably much smaller than in many other large diabetic clinics (table 2). Furthermore, it is noteworthy that in only two cases out of the 36 was a daily dose of protamine zinc insulin in excess of 20 units employed (table 3). This is an indication of our great respect for the hazard of nocturnal hypoglycemic reactions from large doses of protamine zinc insulin, and our belief that most patients who have diabetes of sufficient severity to require more than 20 units of insulin daily maintain better control of glycosuria when they use an insulin having the timing characteristics of appropriate mixtures rather than of protamine zinc insulin alone. In other words, a daily requirement for insulin in excess of 20 units has become in our practice an indication for the

TABLE III  
Doses of Protamine Zinc Insulin

Daily dose	Cases	Per cent
20 units or less	34	94
More than 20 units	2	6
Total	36	100

use of an insulin having timing characteristics intermediate between those of protamine zinc and regular insulin. Obviously, there are a few patients who might be excepted from this policy if experience has shown that they maintain good control of glycosuria and freedom from insulin reactions while taking larger doses of protamine zinc insulin. Nevertheless, in our

experience, these same patients get along equally well with mixtures, and we believe more safely. Indeed, it seems that all patients now treated with protamine zinc insulin would fare equally well with an insulin having timing characteristics intermediate between those of protamine zinc and regular insulin.

It has already been pointed out that in the early days of the use of mixtures it was found by a rather tedious process of clinical trial and error that the best control of severe diabetes and the greatest freedom from insulin reactions were attained with mixtures containing 2 or 3 units of regular insulin for every 1 unit of protamine zinc insulin. The experience of recent years has continued to verify this early impression. The strong effect of such mixtures tends to prevent excessive glycosuria during the day, while the prolonged effect prevents escape from control overnight. There is sufficient

TABLE IV  
Mixtures of Regular and Protamine Zinc Insulin  
in 100 Cases of Diabetes Mellitus

Ratio of regular to protamine zinc insulin	Cases
Less than 1:1	2
1:1 to 1.5-:1	4
1.5:1 to 2-:1	19
2:1 to 2.5-:1	54
2.5:1 to 3-:1	13
3:1 and higher	11

overlapping of the effects of doses on successive days to provide additional insurance against serious loss of control due to the waning of action of one dose before the next one begins to act. The more severe the diabetes, or the higher the carbohydrate content of the diet, the more likely is the ratio to be in the neighborhood of 3:1 rather than 2:1. It will be noted that for 67 of the recent series of 100 patients treated with mixtures, the ratio of regular to protamine zinc insulin was between 2:1 and 3:1 (table 4). With longer periods of observation of the patients the proportion of mixtures in this range would probably be increased, for many of the patients who had mild diabetes and used low ratios at the time of dismissal eventually were stabilized on small doses of protamine zinc insulin alone.

#### DIFFICULTIES IN THE USE OF MIXTURES

It is perhaps unnecessary to point out that mixtures do not solve all the problems of treatment of patients who have diabetes of the type which has been described as "brittle," "labile" or "unstable." The diabetes of a few of these patients remains difficult to control with mixtures or any other form of insulin therapy. While these patients have the most severe type of diabetes from the standpoint of difficulty of control, they do not necessarily



require large doses of insulin. Labile behavior is sometimes observed in diabetic patients who require only 15 to 20 units of insulin daily. For the most part, however, the daily requirement of patients who have labile diabetes is more than 40 units. It can be said without qualification that protamine zinc insulin, used alone, is not good treatment for this type of diabetes. Attempts to treat brittle diabetes with protamine zinc insulin alone almost inevitably lead to two kinds of trouble, namely, poor control of glycosuria during the day when food is being ingested, and hypoglycemia during the night.

Fortunately, some of these patients get over their labile behavior with continued careful treatment, and behave well on conventional management with a combined dose of protamine zinc and regular insulin once daily. Some of those who do not get over it are able to maintain reasonably good control by taking the mixture of protamine zinc and regular insulin in divided doses before the morning and evening meals, about two thirds in the morning and one third in the evening. One dose of globin insulin usually is a failure in these cases, but two doses, one before breakfast and the other before supper, may be as satisfactory as a divided dose of a mixture of protamine zinc and regular insulin. Multiple (three or four) doses of regular insulin seem to be the best expedient in an occasional case, in spite of the inconvenience of such a program of treatment.

The objection is frequently raised that the use of mixtures of protamine zinc and regular insulin is too complicated a procedure for the majority of diabetic patients. We feel that we have been able to overcome this objection in most instances by careful and sometimes prolonged instruction. The majority of patients, in our practice, including those of seemingly mediocre intelligence, are able to master the technic of preparing and injecting the mixtures and adjusting the doses of the two components. In the occasional case in which difficulty is experienced some alternative method of treatment is used which is simpler from the standpoint of the patient, such as globin insulin or multiple doses of regular insulin.

Even though it has been our experience that the majority of patients are able to master the difficulties involved in the use of mixtures in the same syringe, it cannot be denied that this method of treatment is somewhat inconvenient. An escape from this inconvenience in many cases of diabetes would be provided by the availability of a fixed modification of protamine zinc insulin which has an action like that of a 2:1 mixture of regular and protamine zinc insulin. Such a fixed modification is insulin type NPH 50, recently available for trial. This was used in only five cases of the group which has been described. However, before and since this group of cases was seen, experience with NPH 50 has been more extensive and has been reported by Kirkpatrick.<sup>7</sup> We have become convinced that such an insulin, if generally available on the market, would obviate the need for modification of protamine zinc insulin by the patient in many cases, for it fills the needs of the majority of the patients who are now treated with mixtures. Further-

more, it can be expected to give satisfactory results in all the patients who are now successfully treated with small doses of protamine zinc insulin alone. In the few cases of severe diabetes in which higher ratios of regular to protamine zinc insulin are required, supplementation with additional amounts of regular insulin is easily accomplished in accordance with the needs of the individual patient. Fortunately, the addition of small amounts of regular insulin to insulin type NPH 50, unlike the addition to protamine zinc insulin, results in definite intensification of its action.

The principles involved in the adjustment of the two kinds of insulin comprising a mixture are relatively simple. In the first place, as has already been mentioned, it was learned by experience some time ago that the majority of patients who are treated with mixtures of insulin obtain the best control when the amount of regular insulin is two to three times the amount of protamine zinc insulin. In the actual regulation of diabetes of a patient, one can proceed as follows: The test for sugar in a fresh specimen of urine voided in the morning before breakfast is used as a criterion of the adequacy of the dose of protamine zinc insulin taken 24 hours previously. The dose is so adjusted that there will be no nocturnal reactions, and little or no sugar in this specimen, preferably none. Likewise, the test of a fresh specimen voided late in the afternoon before supper serves as an index of the adequacy of the dose of regular insulin taken that morning. This dose is adjusted so that reactions will not occur during the day, and there will be no more than a trace of sugar in this specimen. Changes in the dose of protamine zinc insulin are usually made in steps of 2 units, since this dose is relatively small, while changes in the dose of regular insulin, which is usually at least twice as large, are usually made in steps of 4 units. The patients are carefully instructed in the method of adjustment, for frequently further adjustments of the dose are necessary at home, particularly if the period of observation under the direct supervision of the physician is short.

### SUMMARY

The timing characteristics of appropriate mixtures of protamine zinc and regular insulin are well adapted to the needs in many cases of moderately severe to severe diabetes. Such mixtures provide the requisite intensity of insulin action during the day when food is being ingested, and a prolonged action of low intensity for maintenance of control of diabetes overnight. An effective proportion in most instances is between 2 and 3 units of regular insulin to 1 unit of protamine zinc insulin.

A fixed modification of protamine zinc insulin having an action like that of a 2:1 mixture of regular and protamine zinc insulin such as insulin type NHP 50, could be employed with satisfactory results in many more cases than the standard protamine zinc insulin which is now available. Its action could be further intensified and shortened by the addition of regular insulin when necessary.

## BIBLIOGRAPHY

1. SPRAGUE, ANNE W., and FOLEY, MARY A.: The education of the diabetic patient, *Hosp. Management*, 1940, 1, 41-44.
2. COLWELL, A. R.: Nature and time action of modifications of protamine zinc insulin, *Arch. Int. Med.*, 1944, lxxiv, 331-345.
3. MACBRYDE, C. M., and ROBERTS, H. K.: Modified protamine zinc insulin: an improvement on standard protamine zinc insulin; comparative studies on 62 diabetic patients, *Jr. Am. Med. Assoc.*, 1943, cxxii, 1225-1231.
4. PECK, F. B.: Insulin mixtures and modifications, *Proc. Am. Diab. Assoc.*, 1946, vi, 273-300.
5. LAWRENCE, R. D.: The treatment of insulin cases by one daily injection, *Acta med. Scandinav.*, 1938, xc, 32-53.
6. RICKETTS, H. T.: Does hyperglycemia harm the diabetic patient? *Med. Clin. North Am.*, 1947, xxxi, 267-277.
7. KIRKPATRICK, N. R.: Experience with a new insulin, *Proc. Staff Meet., Mayo Clin.*, 1949, xxiv, 365-370.

# SUMMARY OF EVIDENCE RELATING LIFE SITUATION AND EMOTIONAL RESPONSE TO PEPTIC ULCER \*

By STEWART WOLF, M.D., *New York, N. Y.*

THE evidence connecting the occurrence and recurrence of peptic ulcer to emotional conflicts in the life situation has been recently reviewed by Wener and Hoff.<sup>1</sup> The relationship has not as yet been definitely established, but on the basis of studies from several points of view and with a variety of technics, it seems highly likely that some peptic ulcers, at least, occur as part of a biologic pattern which is set in motion in reaction to stresses and strains involving chiefly problems of interpersonal relationship. The data in support of this view are outlined briefly below.

First, it has been known for many years that the stomach of the subject with duodenal ulcer is a hyperfunctioning one, that is, it is red, secretes relatively large amounts of acid, is relatively hypermotile and empties in a comparatively short time. When it has been possible to induce experimental peptic ulcer in animals, the condition has been preceded and accompanied by intense engorgement of the gastric mucosa.<sup>2, 3, 4</sup>

In our studies on the fistulous subject, Tom, we found by direct observation of the gastric mucosa and simultaneous collections of gastric juice and recording of motility that this hyperfunctioning state could be induced by situations which engendered anxiety associated with feelings of hostility and resentment.<sup>5</sup> We found, moreover, that the stomach under these circumstances was hyperemic, turgid and engorged. When, under circumstances of sustained resentment, this pattern of gastric hyperfunction was prolonged, the pain threshold of the stomach was significantly reduced. This led to localized epigastric pain following the application of stimuli such as pinching or Faradic current, which were ordinarily non-noxious. Likewise, gastric contractions of a force and magnitude which would ordinarily not arouse sensations became painful. Thus, in the absence of ulceration but in the presence of sustained gastric hyperemia and hyperfunction, the characteristic ulcer symptoms of epigastric pain relieved by food or alkalis were frequently observed.

Not only was lowering of the pain threshold observed to accompany gastric hyperfunction in association with sustained conflict, but a second physiologic hazard was also observed under these circumstances, namely, increased fragility of the mucous membrane. When the stomach was in an

\* Presented at a Panel Discussion, Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 29, 1949.

From the Department of Medicine of Cornell University Medical College and the New York Hospital, New York, N. Y.

Aided by grants from the Commonwealth Fund and the Estate of Lester N. Hofheimer.

average state of activity and the membrane relatively pale and flat, it was possible to strike it sharply with a blunt glass rod or draw a dry gauze square over it without producing any visible lesion. In association with sustained hyperemia, however, such minor traumata resulted predictably in small erosions and bleeding points. Indeed, not uncommonly, such erosions and bleeding points appeared spontaneously in association with a period of unusually vigorous contractile activity. One such spontaneously occurring erosion was kept in contact with gastric juice with a titratable total acid of 90 for half an hour. Mucus accumulated rapidly in the region, but it was removed at frequent intervals by suction through a small glass tube. The acid gastric juice was then reapplied to the bare mucosa. A sharp acceleration of acid and concomitant hyperemia of the whole stomach mucosa occurred and persisted for half an hour after the submersion of the hemorrhagic lesions was discontinued.

*Comment.* In this phenomenon may lie an explanation of the persistent hyperacidity regularly encountered in persons suffering from gastritis and peptic ulcer. The fact that the base of the ulcerated lesion which is constantly bathed in acid gastric juice effects a further stimulation of acid secretion indicates that afferent impulses subserve this reflex without sensation resulting. It is likely, however, that pain would follow an adequate chemical stimulus.<sup>6</sup>

*Experimental Production of Ulcer.* The most peripheral edge of the collar of mucosa which lay exposed on the abdominal wall lacked adequate protection owing to defective formation of mucus in this region. A small erosion which occurred on this peripheral edge was exposed continuously to the digestive action of gastric juice for four days. During the first 24 hours, the denuded surface increased in size. It bled intermittently. At the end of four days, it exhibited the typical punched-out appearance of a chronic peptic ulcer, with well-defined edges and a granulating base. It measured approximately 4 mm. in diameter, 1 mm. in depth, and was growing rapidly (figure 1). Traction or pressure on this lesion resulted in pain of a dull, gnawing character, localized in the region of the lesion itself. Throughout the four-day period, the whole mucosa was relatively engorged, and the rate of acid secretion significantly elevated. At the end of four days, because of the hazard to the subject, it was felt that the experiment could not be allowed to continue. The ulcer and surrounding area were covered with a protective petrolatum dressing. Within three days, complete healing had taken place leaving no trace of the lesion behind.

*Mechanism of Gastric Hyperfunction.* The pathways whereby the impulses reach the stomach which induce potentially harmful gastric hyperfunction associated with situational conflicts are unknown, but have been suspected of lying in the vagus nerves. The clinical evidence derived from the practice of vagotomy for peptic ulcer supports this view, since healing has taken place and a negligible number of ulcers have recurred following sur-

gical procedures considered to have divided all of the parasympathetic innervation to the stomach. Additional confirmation derives from an experiment performed in our laboratory on a second fistulous subject whose fistula was made prior to the attempted surgical removal of a carcinoma of the esophagus.<sup>7</sup> During the latter procedure, it was necessary to section the vagus nerves above the diaphragm. Thus, direct observations were available on the stomach before and after vagotomy. Experimental procedures similar to those performed on Tom were carried out on this subject, his gastric mucosa being viewed through a Brown-Buerger cystoscope. During one of the experimental periods prior to vagotomy the appearance and manner of the subject indicated a sharp change from his usual, quiet friendliness. His face was red, and he appeared exasperated and irritable. He had complained of stiffness and back pain ever since the previous experiment, and confessed that he was angry at having come down to the laboratory again in view of the apparent delay occasioned in his operation.

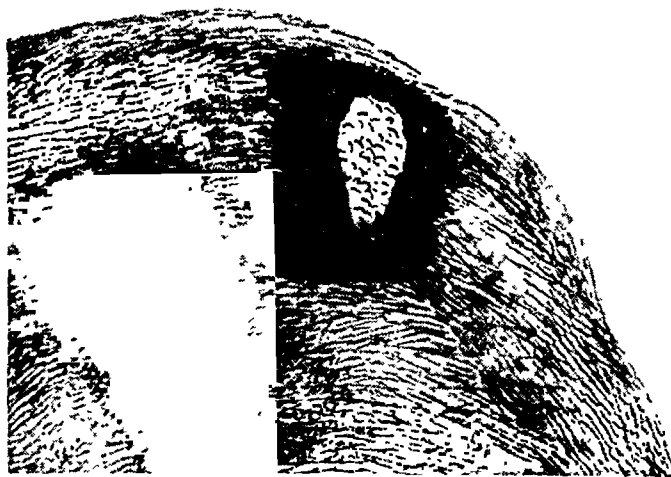


FIG. 1. Drawing of ulcerated lesion induced experimentally on the gastric mucosa of Tom.

The subject's stomach was examined and found to be much redder and more engorged than before, about 70 on the scale in contrast to the previous 50. He was more voluble and talkative. Asked about his concern regarding his condition, he said that he was reminded of the first doctor whom he had consulted for difficulty in swallowing. The latter had focused his attentions on the stomach, much to the annoyance of the patient. "He was so dumb. I told him it wasn't my stomach, because I knew I couldn't swallow right. He made me waste four weeks fooling around." On this occasion, there occurred much more spontaneous motor activity in the stomach than before. The mucous membrane was so turgid that the minor traumata incident to the instrumentation with the cystoscope caused bleeding. The subject's dominant mood during this interview was anger coupled with hostility and strong feelings of frustration. His stomach displayed the pic-

ture of hyperactivity so characteristically found in the subject, Tom, during situational conflicts productive of aggressive attitudes.

Approximately three weeks following vagotomy, an opportunity was afforded to repeat these observations under similar circumstances. On the third experimental occasion following vagotomy, the membrane was pale, 40, and the folds appeared especially thin. After the baseline observations, an attempt was made, as before, to induce anger and resentment in the subject by discussion of the doctor who had failed to diagnose his condition when he first consulted him. As on the occasion prior to vagotomy, he appeared to become significantly angered, with flushing of the face, loud voice and aggressive gestures, "I think he is crazy. I only went to him because he is around the corner. He said the lining was off my stomach, and gave me some stuff that made me feel lousy—last winter I had some crushed toes. He messed them up, too. He's a God-damned quack, and exile. He charged me enough—\$8 a treatment. I'll tell him off." During this outburst, the patient's stomach was continuously under observation through the cystoscope, but, despite the redness of his face, there occurred no detectable change in the appearance of his gastric mucosa (figure 2).

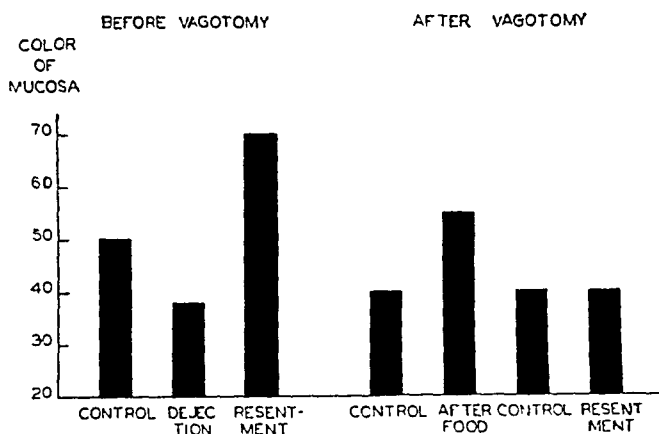


FIG. 2. Changes in the appearance of gastric mucosa under various circumstances before and after vagotomy. Note that vagotomy does not abolish the chemically mediated hyperemia associated with eating.

*Comment.* A negative result with failure of the stomach following vagotomy to become engorged during anger in this single case does not necessarily implicate the vagus as a route by which impulses reach the stomach which are responsible for gastric hyperfunction occurring in response to situational threats. Further evidence leading to this inference, however, has been adduced by Szasz et al.<sup>8</sup> that an acceleration of acid secretion in subjects with peptic ulcer could be induced by arousing them to anger, but that such an acceleration of acid secretion did not occur following vagotomy.

*Clinical Peptic Ulcer.* Although the above data establish the fact that

transitory and even sustained alterations in gastric function occur in company with emotional conflicts and that such changes may be associated with epigastric pain, it remains to correlate such reactions to stress with gastric changes and symptoms in subjects with the actual clinical peptic ulcer. The coincidence of onset and exacerbation of the ulcer syndrome in association with difficult life situations is a familiar bedside observation. Mirsky and associates have shown an increase in concentration of a proteolytic enzyme in the blood and urine of subjects with peptic ulcer and especially in situations of significant personal conflict.<sup>9</sup> Experimental correlation of conflict with gastric hyperfunction and symptoms was reported by Mittelman and Wolff<sup>10</sup> and more recently additional evidence on this point has been collected as detailed below.

*Case 1.* A 44 year old civil service employee had complained of gnawing epigastric pain on and off for 20 years. His father had been a gentle, retiring person and his mother a matriarchal woman, intensely ambitious for her children. His two older brothers were able to adjust satisfactorily to this setting, the oldest by graduating from medical school, the second one by adopting a rebellious attitude and becoming a professional gambler instead of a lawyer as his mother had wished. The patient felt the need to compensate for his brother's indifference, and took pre-medical work in college. He did poorly, and tried engineering instead. After failing that, he abandoned college. In this setting, he had his first symptoms of epigastric pain, and a duodenal ulcer was demonstrated by radiologic examination. He later obtained a civil service job as a draftsman, and became engaged to a warm, sympathetic girl. Symptoms disappeared during this interval, until the girl died of rheumatic heart disease a few months later. The patient's mother also died at approximately the same time. Within a few months he married an authoritarian, cold and financially ambitious woman. She disapproved of his social relationship with men friends, and eventually forced him to give up lodge activities, from which he derived great satisfaction. Shortly after his marriage, the patient's ulcer symptoms recurred, and they have remained chronic ever since. Several exacerbations and two episodes of hemorrhage have coincided with periods in which his wife seriously disparaged his competence as a man. The following experiment, shown graphically in figure 3, illustrates the relevance of his conflicts concerning his wife to his gastric disturbance.

Ten minutes after the end of a spontaneous period of vigorous gastric motor activity and during a period of almost complete absence of contractions, an interview was undertaken in which the patient was reminded that, in contrast to the high regard in which he had been held by his lodge associates, his wife considered him inadequate as a provider, companion and sexual partner. He became grim and tense, clenched his jaws frequently and said, "it's been a fight all along, and now I got no more fight left in me. I'm caught like a rat in a trap." Promptly, forceful gastric contractions began, and by the end of the interview, a state of incomplete tetanus had been established. Acid secretion was also greatly enhanced, exceeding the level observed during the earlier period of spontaneously increased gastric function. By this time, the subject had begun to groan with pain. Shortly thereafter, during attempts at reassurance and diversion, the evidences of gastric hyperfunction subsided, and with them the symptoms.

*Case 2.* A 34 year old Italian income tax collector had his first episode of ulcer pain at age 16 in a setting of conflict with his father over retaining a job as auto paint sprayer, which he considered beneath his capabilities. The patient had resented his father from an early age. "My earliest recollection is lying awake at night worrying and thinking about the way my father was making sexual advances toward



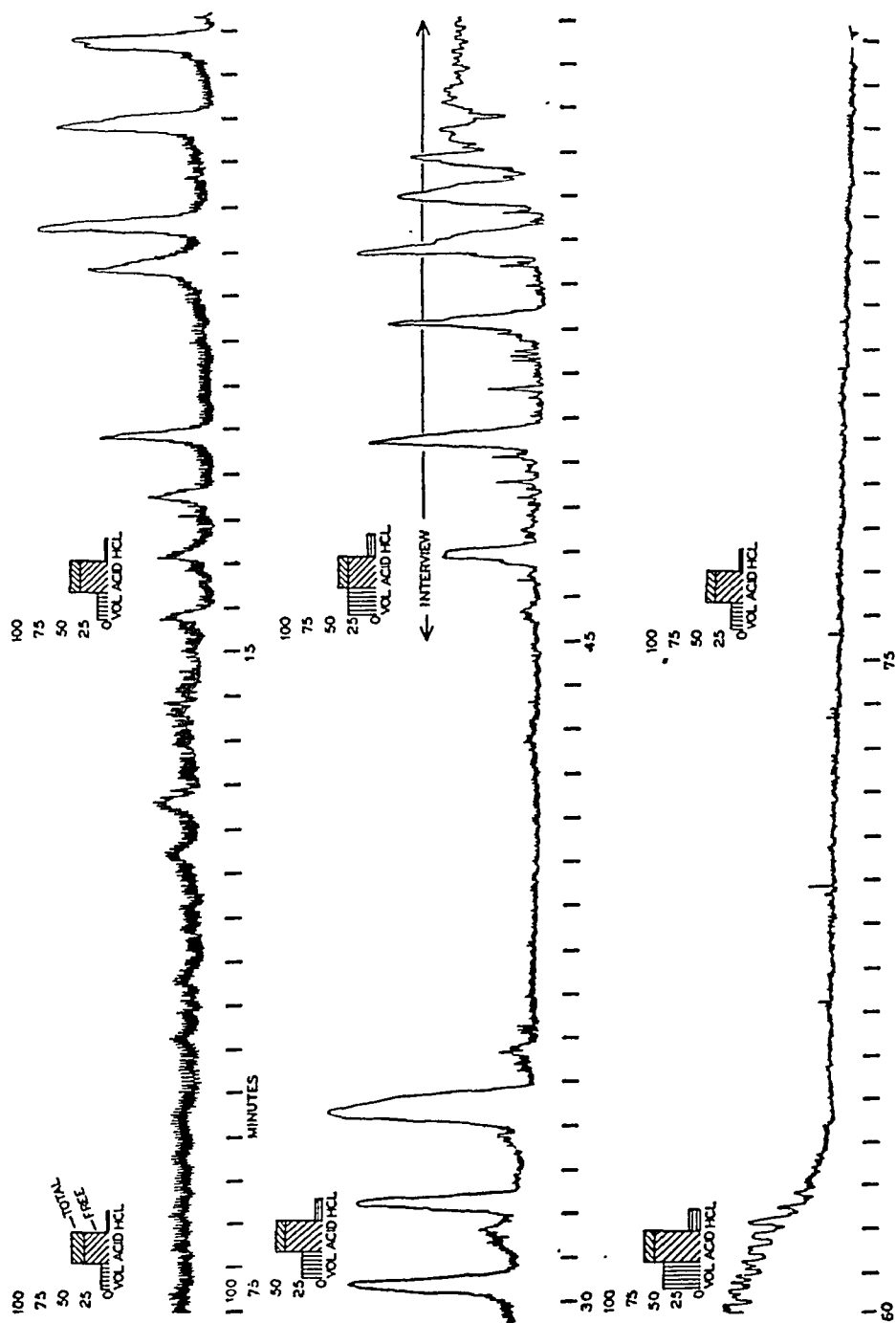


Fig. 3. Changes in motor activity and acid secretion in an individual with peptic ulcer (case 1) during an interview concerning significant personal conflicts.

my mother. I was always relieved if I saw my father go to bed first and my mother stay in the kitchen." The father was a cold, irascible individual who shared the "old country" point of view that a man's sons should work to support him as soon as they could be taken from school. The patient, on the other hand, was eager to go through college and become an engineer. He had grown up in a neighborhood in which there were a good many Jews, and it was a common pattern among the Jewish parents to make unusual sacrifices to provide professional education for their children. Both the patient's father and his younger brother, who also was caught in a conflict between the cultural pattern of his father and his neighborhood, developed peptic ulcers. In addition to his limited educational opportunities, the patient felt that another serious handicap was his small stature. He effected a truculent manner as a child, and got into a great many fights, which he considered "prophylactic," as a means of avoiding being "pushed around" by other people. He could not bear to be laughed at, and was especially sensitive to any slight, real or imagined, to his dignity and competence. He finally obtained a job as an income tax collector, and married an ambitious woman. They had one daughter. He always had difficulty satisfying his wife sexually because of premature ejaculation. She was also dissatisfied with his fixed earnings and lack of progress in the civil service job. The patient noted epigastric pain off and on with exacerbations during periods of stress and conflict and remissions during periods of relative security. "It makes me worse if anyone crosses me. I tighten up and my stomach hurts. When I can relax my stomach improves." He had a gastrointestinal hemorrhage which occasioned admission to the hospital, when a conflict developed between his wife and his favorite sister. During his period of hospitalization he improved markedly with rest, reassurance and without special attention to diet except for frequent feedings. During an asymptomatic period he was intubated with a recording balloon and a Levine tube for collection of the gastric juice. Specimens were withdrawn every 15 minutes. Free and total acid were determined by the usual colorimetric technics. Hydrochloric acid production was calculated with recourse to the methods of Hollander described elsewhere.<sup>5</sup> The acid values and motility pattern are recorded in figure 4. Fifteen minutes after a period of spontaneous motor activity at a time when the gastric musculature is relatively refractory, a discussion was begun of a humiliating experience which he had had on the ward. "An Italian fellow called me a name in Italian. I'm not a dope that I have to take that. He did it again. Later in the day I was lying in bed with a pain and he said 'This is a hell of a time for you to be lying in bed.' I told him it was none of his business, and not to bother me. Now he won't speak to me, and that's what I want. I think I'm entitled to the same respect I give out. Whenever anyone makes a crack at me I have two of them to throw back. I think I'm pretty sharp about solving problems." During the discussion, he was tense, restless and red-faced. Vigorous motor activity occurred and increase in acid output associated with epigastric pain. After approximately 25 minutes, the patient was strongly reassured and the conversation was turned to diverting topics. The gastric motor activity stopped and the pain subsided.

*Case 3.* A 47 year old Jewish lawyer had had peptic ulcer for 23 years. He was the only child of Russian immigrant parents. The father was a quiet, reflective, religious man, but the mother was intensely ambitious and hard-working. She and the father made severe financial sacrifices to provide the patient with an education. He did well in college and law school, and during the course of these years he changed his name to a more easily pronounced, anglicized form. He also married a Roman Catholic girl. His parents disapproved of this marriage, but condoned it, their principal concern being their son's "success in his career." Shortly after graduation from law school, he was taken into a firm of all gentile lawyers. He soon became heavily relied upon, and was doing much of the difficult work of the office. The partners persistently failed, however, to admit him to the firm. This was the source of great disappointment

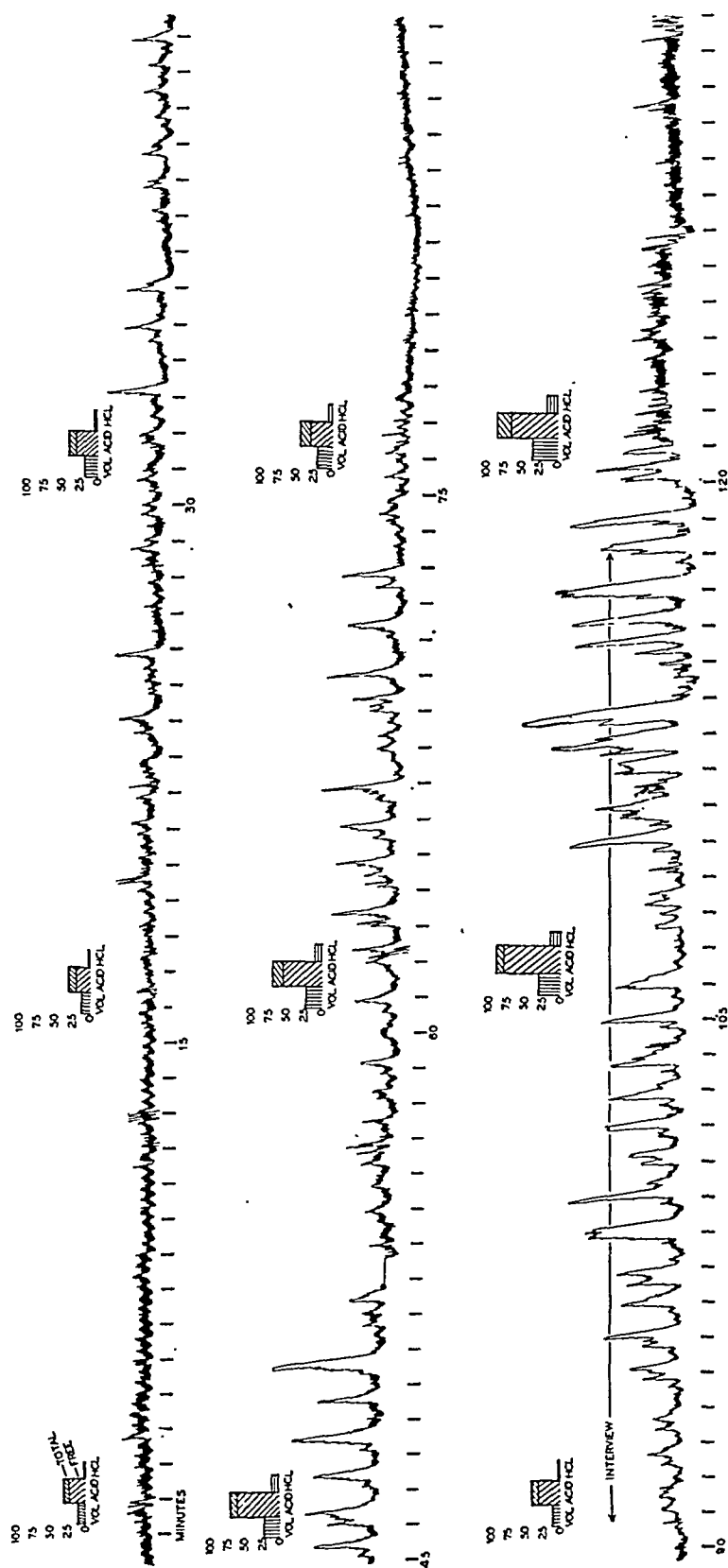


FIG. 4. Changes in motor activity and acid secretion in an individual with peptic ulcer (case 2) during an interview concerning personal conflicts.

and frustration, not only to himself but to his mother and wife, who, like his mother, was intensely ambitious. It was in this setting that ulcer symptoms first developed.

Finally, when it appeared that the partners could no longer exclude him from the firm, they hired a second Jewish lawyer. The head of the firm then told the patient that he felt unjustified to take one of these men and not the other into the firm. This occasion was followed by a severe episode of gastrointestinal bleeding, for which the patient was hospitalized. Finally, at the outbreak of World War II, the younger Jewish lawyer was taken into the Army. The older members of the firm were often preoccupied with matters outside the office, and thus the patient's duties and responsibilities were redoubled. He was virtually running the law office. Despite the heavy work and long hours, his ulcer symptoms disappeared, and throughout the period of the war he felt well. At the conclusion of the war, however, his associate returned from service unharmed, and again the frustrating situation was resumed. The patient's epigastric pain recurred and became incapacitating, and again he was admitted to the hospital. After a few days of rest, encouragement and strong reassurance, and while taking alkalis and frequent feedings, his symptoms again subsided.

At this point, he was intubated with a balloon attached to a kymograph. Gastric motor activity of an average type was recorded until suddenly an interview was engaged in in which the patient was asked why he had failed to meet his mother's ambitions and whether or not he felt that her sacrifices in his behalf had been justified. Almost immediately, gastric contractile activity became enhanced. He showed no evidence of tension or "nervousness" at first. He gave a restrained, well-organized and forceful justification of his life. As the account proceeded, however, his voice became stronger, and he became restless and tense, and the gastric contractions were associated with localized epigastric pain. The interview was allowed to continue for one hour and 30 minutes, when he was given 0.3 gm. of sodium amytal intravenously. At this point, gastric contractions stopped abruptly. His pain was promptly relieved, and his entire manner was altered. He clung weeping and sobbing to the examiner's hand, saying "I've tried so hard, so hard." He said that he finally felt relaxed, and was weeping with relief. After 27 minutes of freedom from pain, and while still under the influence of sodium amytal, a second interview was begun in which it was suggested that his change of name, his marriage to a Roman Catholic and his association with a gentile firm might represent an attempt to escape from identification with Judaism. Again his manner became restrained, his flow of conversation even and forceful. Gastric contractions were resumed, and although they were of much smaller magnitude, they were nevertheless painful.

*Comment.* These experiments on subjects with peptic ulcer in which painful gastric hyperfunction was induced or interrupted by appropriate manipulation of the situation established fairly clearly a relationship between the gastric disturbance and the attitudes and emotions of the subjects. They indicate that these individuals react habitually to stress with an acceleration of gastric function. They do not prove that peptic ulcer is caused by such sustained gastric hyperfunction, but they support this view. Further data were adduced from study of a fistulous human subject who happened also to have a peptic ulcer.

*Case 4.* A 67 year old Merchant Marine tug boat chief engineer developed obstructive symptoms with persistent vomiting and emaciation three weeks prior to his admission to the hospital. He had noted weakness and vague epigastric discomfort but he had had no history of pain suggestive of peptic ulcer except for a brief episode 30 years before which lasted only a few weeks. Roentgen-ray examination, however,

demonstrated an ulcer with gross distortion of the duodenal cap. The stomach was dilated and emptying greatly delayed. Free acid in the gastric juice was 15 and total 38. Stools were negative for occult blood but red cells in the peripheral blood numbered only 3.4 million with 11.5 gm. hemoglobin. An exploratory operation confirmed

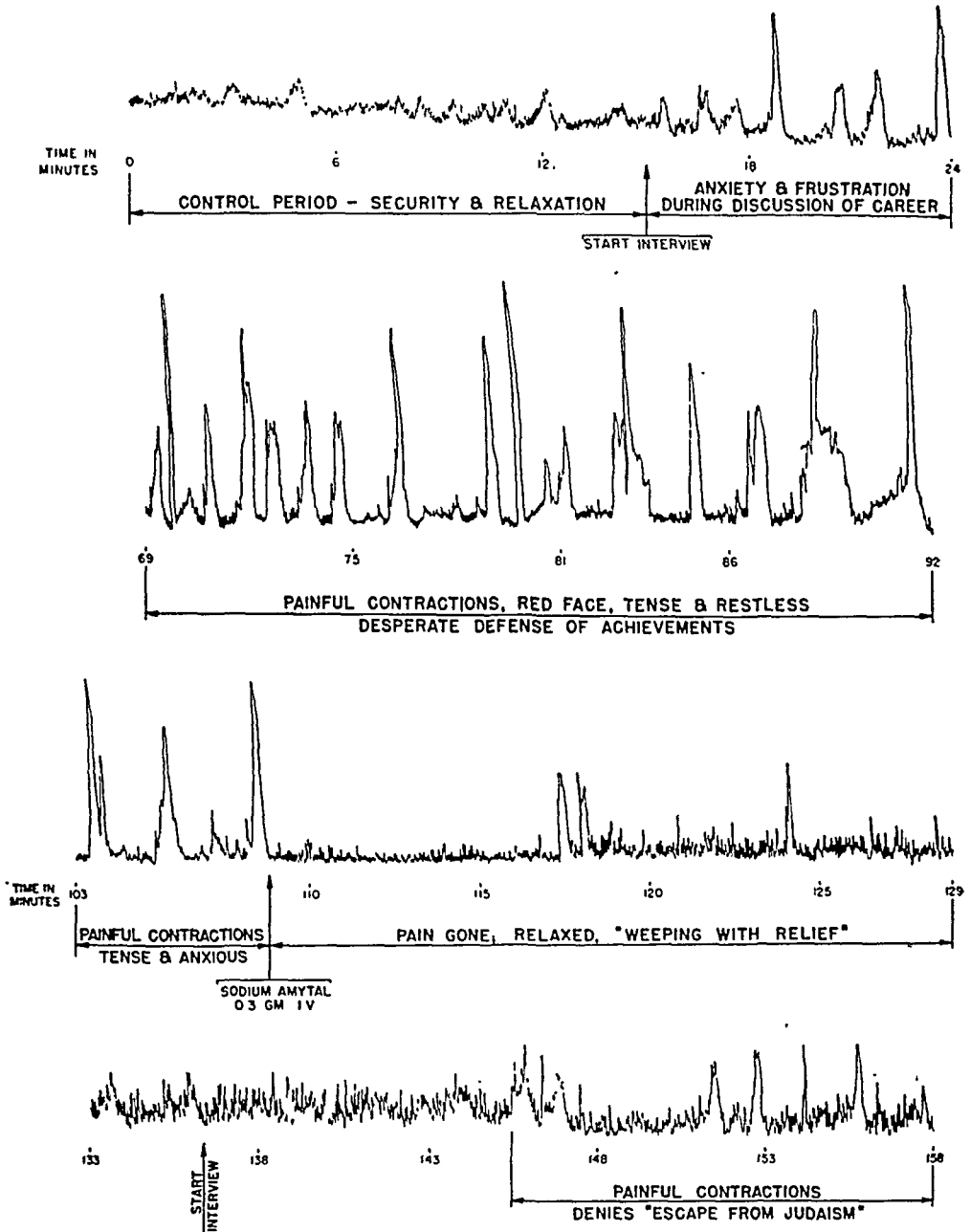


FIG. 5. Changes in motor activity in a subject with peptic ulcer (case 3) during an interview concerning significant personal conflicts.

the presence of the obstructive ulcer in the region of the duodenal cap. A posterior gastroenterostomy was performed to relieve the obstruction and post operatively a Miller-Abbott tube was left in place. The latter apparently damaged the esophagus in some way because a progressive narrowing with final occlusion of the esophagus oc-

curred over a period of three weeks. Because of the esophageal stricture a gastrotomy was done. The stoma measured approximately 5 cm. in diameter and through it herniated parts of a few engorged gastric rugae. It was accordingly possible to study this subject in the same manner in which experimental observations were made on Tom and published in detail elsewhere.<sup>6</sup>

The experiment was carried out 13 hours after the last feeding and with the subject reclining comfortably on a couch. The gastric mucosa was continuously observed under standard lighting conditions. Gastric juice was siphoned through a Levine tube and motor activity was recorded on a kymograph from an inlying inflated balloon. During approximately 45 minutes of control period the subject was lightly diverted and continuously reassured. As already noted the membrane during this period was already moderately engorged (3+) and hyperemic (60 on the color scale). Gastric juice was elaborated at the rate of approximately 20 c.c. every 15 minutes, was moderately viscous and opaque with free acid remaining in the neighborhood of 15 units. Abruptly he was asked whether or not his own and his wife's ambitions had been satisfied by his becoming a tugboat engineer. His manner became serious and slightly grim, but he maintained that the work had been entirely satisfactory. He was then asked where a tugboat engineer stood in the social constellation of men who had qualified as chief engineers. His even manner continued although tension was evident by this time and he wiped a tear from each eye. He was further asked about possible conflicts with his wife. He denied conflicts but the denial was associated with additional lacrimation and within one-half hour of the start of this interview the gastric rugae had become intensely red (80) and engorged, completely filling the area of the stoma. Motor activity became intense and sustained and free acid rose to 35 units. No pain was noted.

*Comment.* This experiment provides direct visual confirmation of the findings detailed above in patients with peptic ulcer in whom the contemplation of relevant personal conflicts was associated with intense gastric hyperfunction and often symptoms.

*Nature of the Personality Reaction.* Numerous attempts have been made to explain why some individuals in a setting of significant emotional conflict develop troublesome gastric hyperfunction and perhaps peptic ulcer, while others may develop precisely the opposite changes in the stomach with hypoacidity, slow emptying and nausea and still others develop other physiologic disturbances but no evidence of gastric disorder. Analysis of the conflict situation has not been fruitful, and neither have attempts to construct a constitutional or personality profile been successful in delineating very sharply between those who develop and those who do not develop peptic ulcer. It has been more profitable to examine and characterize the way in which the individual habitually met threats and challenges in his life situation. The subject with peptic ulcer may feel passive and have strong dependent needs as has been pointed out by Alexander<sup>11</sup> and numerous others,<sup>8, 12, 13</sup> but his behavior is aggressive. He must appear master of the situation in contrast to the subject with gastric hypofunction, who readily assumes a passive rôle in human relationships.<sup>14</sup> The gastric hyperfunction itself implies a need to be fed and sustained, but it is an aggressive biologic response which in animals including man precedes the act of devouring. It is thus in keeping with the general behavior reaction of competitive aggression. These features have been reviewed elsewhere.<sup>5, 10, 11</sup> One probably could not answer in simple

terms why a human organism elects a defensive reaction pattern of gastric hyperfunction which when sustained may be self-destructive. It would be similarly impossible to attribute exclusively to either constitution, temperament or experience, the selection by a man who has felt on his face the glove of an adversary any of the several possible courses of action open to him. It has been pointed out elsewhere that he can choose pistols, sabres or boxing gloves, or he may elect to run away, to collapse at the feet of his challenger or sidestep the incident by retracting or making a joke of it.<sup>15</sup> Why he chooses one course rather than another depends upon a myriad of factors including his inherited tendencies, his early experiences, his cultural background, his habits and skills, etc. The significant question for present consideration is the character of the pattern which he does select and what its implications are for his health and survival.

### CONCLUSION

The cause and mechanism of peptic ulcer are still unexplained, but a large body of experimental evidence supports the view that this disorder, in many instances at least, occurs as a sequel to disturbed gastric function in reaction to significant stresses in the life situation. The steps which support this formulation are briefly as follows:

1. The stomach in peptic ulcer is hyperfunctioning as regards engorgement, blood flow, acid production, motor activity and emptying time.
2. Gastric hyperfunction accompanied by epigastric pain of typical "ulcer" type may be induced in human subjects by exposure to situations involving significant personal conflict.
3. Such gastric hyperfunction is apparently mediated through vagus innervation, and is associated with two serious physiological hazards: (a) a lowering of the pain threshold in the stomach, and (b) increased fragility of the membrane.
4. Gastric juice kept in close contact with a minor erosion leads to further gastric hyperfunction and may result in the establishment of an ulcer.
5. In subjects with peptic ulcer gastric hyperfunction may be accentuated with the production of hyperacidity, hypermotility and pain by a vigorous discussion of significant personal problems.

### BIBLIOGRAPHY

1. WENER, J., and HOFF, H. E.: The neuro-humoral aspects of peptic ulcer formation, *Canad. Med. Assoc. Jr.*, 1948, lix, 115.
2. HALL, G. E., ETTINGER, G. H., and BANTING, F. G.: An experimental production of coronary thrombosis and myocardial failure, *Canad. Med. Assoc. Jr.*, 1936, xxxiv, 9.
3. MANNING, G. W., HALL, G. E., and BANTING, F. G.: Vagus stimulation and the production of myocardial damage, *Canad. Med. Assoc. Jr.*, 1937, xxxvii, 314.
4. VARCO, R. L., CODE, C. F., WALPOLE, S. H., and WANGENSTEEN, O. H.: Duodenal ulcer formation in the dog by intramuscular injections of a histamine beeswax mixture, *Am. Jr. Physiol.*, 1941, cxxxiii, 475.

5. WOLF, STEWART and WOLFF, H. G.: Human gastric function. An experimental study of a man and his stomach, 2nd ed., 1947, Oxford University Press, New York.
6. PALMER, W. L.: Mechanism of pain in gastric and in duodenal ulcer, *Arch. Int. Med.*, 1927, xxx, 109.
7. WOLF, STEWART and ANDRUS, W. D.: The effect of vagotomy on gastric function, *Gastroenterology*, 1947, viii, 429.
8. SZASZ, T. S., KIRSNER, J. B., LEVIN, E., and PALMER, W. L.: The role of hostility in the pathogenesis of peptic ulcer: Theoretical considerations with the report of a case, *Psychosom. Med.*, 1947, ix, 331.
9. MIRSKY, I. A.: Title at Am. Psychosom. Soc., *Psychosom. Med.* In press.
10. MITTELMANN, B., and WOLFF, H. G.: Emotions and gastroduodenal function, *Psychosom. Med.*, 1942, iv, 5.
11. ALEXANDER, F.: Clinical notes: Treatment of a case of peptic ulcer and personality, *Psychosom. Med.*, 1947, ix, 320.
12. HEIDE, CAREL VAN DER: A study of mechanisms in two cases of peptic ulcer, *Psychosom. Med.*, 1940, ii, 398.
13. DUNBAR, FLANDERS: Emotions and bodily changes, 1946, Columbia University Press, New York.
14. WOLF, STEWART: Observations on the occurrence of nausea among combat soldiers, *Gastroenterology*, 1947, viii, 15.
15. WOLF, STEWART, PFEIFFER, J. B., RIPLEY, H. S., WINTER, O. S., and WOLFF, H. G.: Hypertension as a reaction pattern to stress; summary of experimental data on variations in blood pressure and renal blood flow, *Ann. Int. Med.*, 1948, xxix, 1056.



## CALCAREOUS PANCREATITIS \*

By CASIMIR A. DOMZALSKI, JR.,† M.D., *Detroit, Michigan*

PANCREATIC calcification of all types is relatively rare. In a recent review of 10 large series of autopsy reports, Pascucci found pancreatic calcification reported in only 52 cases (0.044 per cent) of an aggregate total of 117,031 autopsies.<sup>1</sup> When looked for carefully, however, the incidence of pancreatic calcification rises more than a hundredfold, as was shown by Ludin, who carefully dissected each pancreas which showed heavy shadows in a postmortem roentgenogram. He found calcifications in 28 of 542 organs, an incidence of 5.3 per cent.<sup>2</sup>

The clinical incidence of pancreatic calcification, especially in recent years, is higher than one would be led to expect from autopsy reports. Up to the year 1946 there were 243 cases of pancreatolithiasis reported,<sup>3</sup> of which 15 per cent had appeared in the last 14 years. Diffuse parenchymal pancreatic calcification, a much rarer condition, had been reported only 20 times, roughly half of these in the last four years. Fourteen additional cases of the latter were reported in 1946 by Comfort and his associates.<sup>4</sup>

Pancreatic calcification falls naturally into three categories: (1) Calcifications in the form of stones lying free in the ducts of Wirsung and Santorini and their tributaries. Ranging in size from "gravel" to solitary stones weighing as much as 60 grams,<sup>5</sup> they may be mulberry-shaped or have sharp edges with a propensity for erosion either into blood vessels with gross and occasionally fatal intestinal hemorrhage,<sup>6</sup> or into the abdominal cavity. They are composed chiefly of calcium phosphate and carbonate, and vary in color from gray to brown depending on the amount of bile-staining which has occurred. (2) Diffuse parenchymal calcifications, distributed throughout the gland in the interstitial tissue and in the dense connective tissue which ultimately replaces most of the glandular tissue in a chronically inflamed pancreas. (3) Mixed calcification of the pancreas, featuring both parenchymal and free intraductal calcifications. While it is not possible clinically to differentiate which type is present, it is frequently possible to do so by roentgen-ray. From the standpoint of treatment such a differentiation is important, since complete relief might be expected from surgical intervention in pure calculous disease, whereas treatment should be medical in cases of diffuse calcification with pancreatic insufficiency. This insufficiency may be endocrine, in the form of diabetes mellitus, or exocrine, in the form of steatorrhea and creatorrhea, or both.

Two cases of diffuse pancreatic calcification which were seen during the past year at Queen's Hospital are reported because of their relative rarity and because several striking clinical features were common to both cases.

\* Received for publication March 5, 1947.

† Formerly Resident in Medicine, Queen's Hospital, Honolulu, T. H.

## CASE REPORTS

*Case 1.* A 43 year old Irish-Hawaiian male was first admitted to Queen's Hospital July 12, 1945, with a chief complaint of weakness. He had diabetes and had been taking insulin "off and on" for one year. During this period he had developed a persistent diarrhea, had lost about 70 pounds, and had become very weak. He described his stools as being large and yellow, with "droplets of oil" on the surface of the water after an evacuation.

His past history included measles, mumps, and chickenpox in childhood, and pneumonia at the age of 27. The only previous gastrointestinal disturbances he had ever experienced were three bouts of severe epigastric pain many years previously, which the patient attributed to over-indulgence in alcohol. His father had had diabetes and died at the age of 54. His mother had died of a "stroke" at the age of 72. There was no other history of diabetes in the family

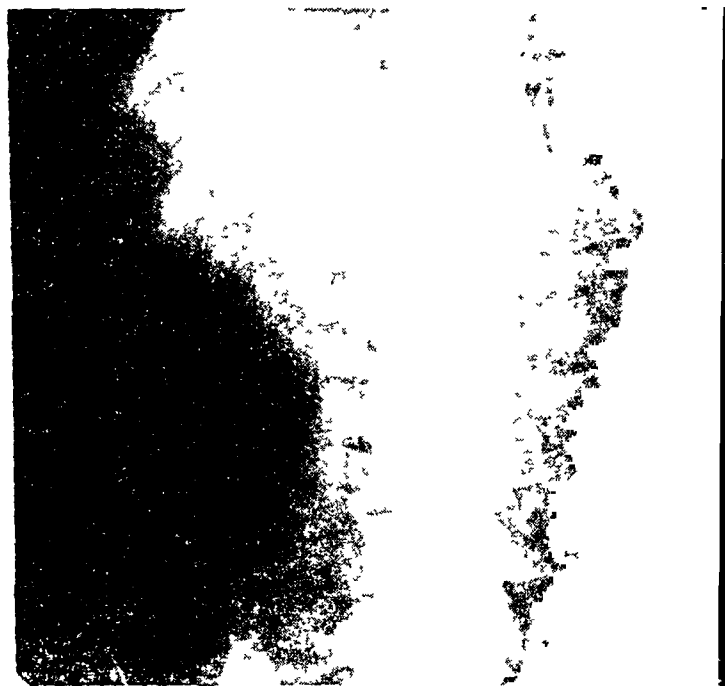


FIG 1. Roentgen-ray of the abdomen, case 1, showing multiple calcifications in the head and tail of the pancreas.

Physical examination revealed a tall, gaunt male who appeared chronically ill. There were slight reddening and atrophy of the tongue, and tiny fissures at the corners of the mouth. The remainder of the examination was essentially negative except for evidence of rather marked weight loss. Admission blood count showed 5,180,000 erythrocytes, 13 gm. of hemoglobin, and 16,150 leukocytes, with 42 per cent polymorphonuclear leukocytes and 58 per cent lymphocytes. The urinalysis was negative and the blood sugar was 158 mg. per cent. A stool examination showed a large number of striated muscle fibers and 16 per cent of the dry weight was fat.

A barium enema revealed a normal colon but the roentgenologist noted a large accumulation of calcific deposits in the pancreas. A lateral film of the abdomen confirmed the location of the calcifications. An oral cholecystogram demonstrated a normal gall-bladder. An upper gastrointestinal roentgen-ray study was essentially negative except for a slight compression of the descending and transverse portions of the duodenal loop from without, apparently by the head and body of the pancreas.

This patient's diabetes proved almost impossible to control. His ravenous appetite necessitated a rapid increase in his caloric intake from 1,900 calories a day to 2,500 calories a day. His urine was tested for sugar before each meal and was utterly unpredictable, varying from negative to four-plus for the same meal and same insulin dosage on successive days. Insulin dosage was arbitrarily fixed at 60 units of protamine zinc insulin each morning, after many fruitless adjustments. He was given Syntropan for the epigastric discomfort of which he complained. He had not mentioned this pain on admission, but admitted that he had had it for quite some time. It was not relieved by Syntropan and the medication was discontinued. He was given pancreatin, five grains three times daily, and this dosage was doubled on the eighth day. The diarrhea subsided to one or two stools daily,



FIG. 2. Lateral film of the abdomen, case 1, demonstrating the pancreatic calcifications immediately anterior to the spine.

but these were still bulky and fatty. By the fifteenth day, the patient had gained five pounds, felt much better, and wished to be discharged although his diabetes was still uncontrolled. He was taught how to test his urine for sugar and was discharged with a supply of insulin.

*Second Admission.* The patient returned to the hospital December 3, 1945, again complaining of weakness and weight loss. His weight had fallen to 125 pounds and he had developed a chronic cough. Physical examination revealed much the same picture as at the time of the first admission. The blood count showed 5,100,000 erythrocytes, 10.6 gm. of hemoglobin, and 13,200 leukocytes, with 73 per cent polymorphonuclear leukocytes and 25 per cent lymphocytes, 1 eosinophile, and 1 monocyte. Urinalysis was negative except for a four-plus sugar reaction. The blood

calcium was 9.4 mg. per cent and the blood phosphorus was 2.8 mg. per cent. The blood Laughlen test was negative. Blood amylase was 10 per cent (Fennel's method: 10 per cent to 35 per cent is normal), and the urinary amylase was 2 per cent. A roentgenogram of the abdomen again demonstrated the multiple pancreatic calcifications, and a chest film showed bronchiectasis of the left lower lobe with an associated pleural reaction obliterating the corresponding diaphragm.

Carbohydrate metabolism was still erratic and great difficulty was encountered in stabilizing his diabetes. As he gained weight, however, his insulin requirement gradually decreased from 110 to 40 units of insulin daily. He was given kaopectate and at times paregoric for his diarrhea, as well as pancreatin, one gram three times daily. Amphogel was effective in relieving the sporadic epigastric pain of which he complained. He improved slowly, the cough disappeared, and his weight increased to 146 pounds. He was discharged April 18, 1946.

*Third Admission.* The patient was readmitted July 10, 1946, with a chief complaint of hemoptysis. He had felt well until about 10 days prior to admission, when he contracted a "cold." He developed a cough productive of yellow sputum which later became blood-tinged. A few moist râles at the left apex were the only new finding on physical examination. The blood count was normal except for a slight leukocytosis (11,200), with a normal differential, and the urinalysis was negative except for a four-plus sugar reaction. The blood sugar was 196 mg. per cent. The sputum contained large numbers of tubercle bacilli, and a chest film demonstrated a small reticulated infiltration in the upper lobe of the right lung. A right phrenicotomy was done September 11, 1946, and one week later the sputum was negative for acid-fast bacilli on three successive examinations. His diabetes remained difficult to control and a day-to-day variation of the insulin dosage was necessary. Steatorrhea was still present but responded fairly well to pancreatin and kaopectate, and his weight increased from 134 to 144 pounds. He was transferred to a sanatorium September 28, 1946.

*Case 2.* A 39 year old white male applied for a position as chef at Queen's Hospital in August, 1946. The preemployment chest roentgenogram showed a moderately large pulmonary infiltration in the apical portion of the left lower lobe, probably tuberculous. He was admitted to the isolation unit of the hospital and put on a regimen of strict bed rest. His history revealed that he had had an increasingly productive cough for about three weeks, but no other symptoms. Physical examination was entirely negative. His blood pressure was 120 mm. Hg systolic over 78 diastolic.

There was nothing of note in his past history up to about two years before admission, at which time he had suffered a marked weight loss (approximately 70 pounds in two months), attributed by the patient to the fact that he had just had most of his teeth extracted. However, a Selective Service examination revealed that he had diabetes mellitus. He was rejected and no treatment was undertaken by the patient. Eighteen months prior to admission he had been hospitalized in Los Angeles with a bilateral pneumonia and during his stay in the hospital treatment of his diabetes was carried out. He was taking 40 units of protamine zinc insulin each morning at the time of discharge, and continued to take it regularly until his admission to Queen's Hospital. Chest roentgen-ray at the time of discharge was said to show complete resolution of the pneumonia. A short time before the patient developed this pneumonia, a close personal friend had died of pulmonary tuberculosis. There was no family history of diabetes or tuberculosis.

The sputum was positive for acid-fast bacilli. The sedimentation rate was not elevated. The blood count was normal and the urinalysis was negative. He was put on a daily dose of 55 units of protamine zinc insulin. His appetite seemed to increase steadily, but on the sixtieth hospital day his weight was the same as on ad-

mission, although his caloric intake had been gradually increased to 3,000 calories daily. It was noted during this period that the patient's stools were consistently bulky, pale, and extremely malodorous. He did not complain of diarrhea at any time. An analysis of the stool showed it to be 46 per cent fat (dry weight). Pancreatic steatorrhea was suspected and a roentgen-ray of the abdomen was obtained. This showed extensive calcification throughout the entire pancreas. There was complete failure of visualization of the gall-bladder on oral cholecystography, which was interpreted as demonstrating marked impairment of function of the gall-bladder. There was no roentgen evidence of cholelithiasis. After the patient had received one gram of pancreatin daily for 10 days, a second stool analysis showed that 54 per cent of the dry weight was fat. During the third month of hospitalization this patient was on a diet of 3,250 calories a day, and his insulin requirement had increased to 70 units daily. His weight had increased from 138 to 145 pounds.

At the end of the third month he became despondent over family difficulties and his appetite waned, resulting in a five-pound weight loss. He became moody and intractable and insisted on being released from the hospital. He was discharged against advice December 27, 1946. No insulin was furnished him at discharge.



FIG. 3. Postmortem roentgen-ray of pancreas, case 2, showing replacement of practically the entire gland by calcific deposits.

He was seen by various hospital personnel during the next few days and it was evident that he was drinking heavily. He was readmitted the fourth day after discharge in coma. He appeared pale, moderately cyanotic, and was perspiring profusely. He had had a very large involuntary evacuation. His temperature was 101° F., pulse 90 per minute, and blood pressure 180 systolic over 104 diastolic. The respirations were rapid, deep, and rattling in character. Examination revealed soft eyeballs, loss of all muscle tone, coarse rhonchi throughout the chest, hyperactive heart sounds, and absence of all reflexes, including the corneals. Urinalysis showed no sugar and the blood sugar was 28 mg. per cent. The blood count showed 4,760,000 erythrocytes, 12.2 gm. of hemoglobin, and 38,000 leukocytes, with 91 per cent polymorphonuclears and 9 per cent lymphocytes.

Massive amounts of glucose were given intravenously; within two hours the blood sugar was 92 mg. per cent and within five hours the urine showed a 3-plus sugar reaction. He did not improve and at the end of 12 hours his temperature was 103° and acute pulmonary edema developed. The pulse was 160 per minute and copious amounts of froth poured from his mouth and nose. A venesection was done and Ouabain was given intravenously with dramatic improvement. The following morning the chest was fairly clear and the pulse was down to 120 per minute. He remained in coma in spite of blood sugar levels reaching as high as 600 mg. per cent. There was constant urinary spillage of sugar but acetone bodies did not appear. Moderate doses of regular insulin were given. A lumbar puncture on the third day

revealed entirely normal spinal fluid, and an electrocardiogram on the fourth day was essentially normal except for tachycardia. A serum amylase determination on the fourth day was normal, and the serum calcium was 11.4 mg. per cent. Although his white count slowly fell to 18,000, his fever progressively mounted and he died on the fifth day without having regained consciousness. Penicillin, 50,000 units, had been given intramuscularly every two hours since admission. The clinical diagnoses were insulin shock of irreversible type, such as occurs in about 1 per cent of all patients given insulin shock therapy,<sup>7</sup> and bilateral bronchopneumonia.

At autopsy, the pancreas weighed 80 grams and felt like a bag of pebbles. On section, multiple irregular calcific nodules were found throughout, the largest measuring about 0.5 cm. across. The entire gland seemed to consist of dense connective tissue so that no parenchyma could be identified and the ducts could not be made out. Histologic study showed it to be densely fibrotic connective tissue containing only a few islands of Langerhans, a few duct-like structures, and an occasional small nest of distorted acinar cells. The many calcifications seemed to be deposited around what appeared to be areas of old fat necrosis. The islets which remained were small and in the process of being obliterated by the fibrotic process. The liver weighed 1,750 grams and was firm and smooth, with moderate passive congestion, but no fatty infiltration was detected. The gall-bladder appeared normal, emptied easily, and contained no stones. There was no evidence of fat necrosis in the mesentery or omentum. Three small superficial ulcers, which proved to be tuberculous on histologic examination, were found in the mucosa of the ileum near the ileo-cecal valve. Each lung weighed 720 grams and showed mild congestion and edema, with patchy atelectasis and lobular pneumonia. A well walled-off tuberculous abscess, 2 cm. in diameter, was present in the left apex together with a cicatrizing pleural scar. A similar lesion was found at the hilum of the left lung.

### DISCUSSION

The outstanding clinical features of these two cases of pancreatic calcification were: (1) steatorrhea with marked weight loss, (2) severe, and in one case intractable, diabetes, and (3) complicating pulmonary tuberculosis. It has been generally observed that steatorrhea occurs in only about one-half of all cases of calcareous pancreatitis. It was a prominent feature in both cases reported, although only the first patient actually complained of diarrhea. Pancreatic insufficiency could reasonably be expected from the relatively marked destruction of glandular tissue that was shown by the roentgen-ray, although disturbances of pancreatic function have been absent in about 10 per cent of the reported cases of pancreatic calcification.<sup>4</sup>

Diabetes mellitus, latent or active, is said to occur in about 50 per cent of all cases of pancreatic calcification.<sup>8</sup> This is a much higher incidence of diabetes than occurs when pancreatic damage is due to obstruction of the ducts by a pancreatic calculus. It is well known that when stones obstruct the pancreatic ducts, destruction of the acinar tissue is early, rapid, and quite complete, but the islands of Langerhans survive until very late in the process. Exocrine failure precedes endocrine failure of the pancreas when pancreatic destruction is due to ductal obstruction. No better illustration of this could be cited than the fact that Banting and Best were launched on the investigation which ultimately led to the discovery of insulin<sup>9</sup> by Barron's autopsy report on a patient who had had a pancreatic stone.<sup>10</sup> The pancreas of this

patient showed total atrophy of the acini with preservation of the islets of Langerhans.

However, this does not hold true in case of diffuse parenchymal calcification of the pancreas, and even the reverse may occur: the islets are sometimes destroyed first. The diabetes may appear even before calcareous pancreatitis develops. This occurred in two of Pasternack's cases<sup>8</sup> and in both of our cases. This is not at all difficult to understand when the two underlying pathological processes are separately analyzed. Ductal stones destroy acinar tissue by simple back-pressure and retrograde inflammation secondary to stasis. In contrast, diffuse parenchymal calcification occurs first in the interstitial tissue. This tissue is involved in both acute hemorrhagic pancreatitis, and in acute interstitial pancreatitis as described by Elman<sup>11</sup> and others. The latter type of pancreatitis often masquerades as brief episodes of gastrointestinal upset, with epigastric or generalized abdominal pain, nausea, vomiting, and sometimes diarrhea. The diagnosis rests mainly on the characteristic elevations in the serum amylase and lipase, and is helped when there is pain which radiates to the back or to the left costovertebral angle. Acute interstitial pancreatitis may also be misinterpreted as acute alcoholic gastritis, which is probably what occurred in case 1. He had had three previous bouts of severe epigastric pain accompanied by vomiting, and had attributed them to alcoholic excesses.

Acute pancreatitis of the hemorrhagic type undoubtedly plays an important rôle in the pathogenesis of calcareous pancreatitis. The fat necrosis which is found in acute hemorrhagic pancreatitis is due to a splitting of neutral fat into fatty acids and glycerine by lipase which escapes from the pancreas into the tissues. Insoluble soaps are then formed by the combination of the liberated fatty acids with calcium. The glycerine is absorbed. Edmondson and Fields<sup>12</sup> have demonstrated a moderate fall in the serum calcium of patients with acute pancreatic necrosis, and large amounts of calcium in the pancreatic lesions. A depression of the serum calcium has been reported in several cases of calcareous pancreatitis and occurred in case 2. At autopsy, the pancreatic calcifications were found to be centered around what were probably areas of old fat necrosis.

Comfort et al.<sup>4</sup> have recently demonstrated in a fairly large series of cases that both interstitial and hemorrhagic pancreatitis occur as the acute phases of what they term chronic relapsing pancreatitis. Diffuse calcification developed in 14 of their 29 cases. Chronic relapsing pancreatitis is a disease characterized by remissions and acute exacerbations of either interstitial or sublethal hemorrhagic pancreatitis. Whether both types of acute inflammation occur in the same patient at different times has not been established, but either type has been definitely shown capable of producing chronic pancreatitis with any or all of its sequelae of steatorrhea, diabetes, and calcification. Disturbances in pancreatic function may be transitory, demonstrable only during the acute attack, or permanent. Complete pancreatic failure may be unaccompanied by calcification, and contrariwise, calcification without any

metabolic disturbances has been reported. Calcification may rarely develop painlessly (only one case in Comfort's series). Case 2 was evidently in this category.

It should, of course, be borne in mind that acute interstitial and acute hemorrhagic pancreatitis are distinct entities and may occur only once in the lifetime of an individual. That the latter and chronic relapsing pancreatitis are not identical is highlighted by the fact that diabetes has been found only rarely (2 per cent) to follow acute hemorrhagic pancreatitis,<sup>13</sup> whereas it occurs in 50 per cent or more of all cases of calcareous pancreatitis.

Complicating biliary disease is reported to be fairly common in almost all forms of pancreatic disease. A normal cholecystogram was obtained in the first case, and although abnormal function was reported in the second case, no structural abnormality was discovered at autopsy. Degenerative fatty infiltration of the liver producing a palpably enlarged liver occurs in some cases of chronic pancreatitis, the "pancreato-hepatic syndrome,"<sup>14</sup> most probably due to a deficiency in lipocaic, the pancreatic hormone which regulates the deposition of fat in the liver cells. Hepatomegaly was not present in the first case, and the liver was essentially normal on histologic study in the second case.

A history of alcoholism has often been cited as a salient feature in pancreatic inflammatory disease. It was regarded, however, as a merely coincidental finding until the accumulation of recent evidence, which has pointed to alcohol as at least a frequent precipitating agent if not actually of etiological importance. Carter<sup>15</sup> found tremendously elevated serum amylase values in 11 alcoholic patients with acute abdominal symptoms. Four of the patients were operated upon and acute interstitial pancreatitis was found. Alcohol definitely precipitated acute attacks in 14 per cent of Comfort's cases of chronic relapsing pancreatitis, and 59 per cent of his patients were users of alcohol. This has borne out the observations of earlier writers such as Weiner and Tennant,<sup>16</sup> Myers and Keefer,<sup>17</sup> and Clark.<sup>18</sup> Our first patient was a constant heavy user of alcohol, and the second patient was a sporadically heavy drinker. In a study of 4,000 autopsies, Weiner and Tennant concluded that pancreatic disease is 40 to 50 times as frequent among alcoholics as among non-alcoholics.

Patients with calcifying disease of the pancreas are predisposed to pulmonary complications, and both of our cases developed pulmonary tuberculosis. Two of Pasternack's cases and one of Snell and Comfort's also had pulmonary tuberculosis. Other pulmonary complications, such as bronchopneumonia, abscess, and gangrene have been reported. It is interesting to speculate as to whether or not the metaplasia of the bronchial epithelium resulting in these patients from the loss of vitamin A in the fatty stools<sup>13</sup> is an important factor in predisposing them to pulmonary infections. It appears that the pancreatic insufficiency not only predisposes to pulmonary infection but also has quite a direct bearing on the patient's response to it. The first patient had intractable diabetes and showed relatively little resistance to the



tubercle bacillus. He has been followed since his transfer to the sanatorium, and generalized pulmonary spread of the tuberculosis is developing. The second patient had easily controlled diabetes and his pulmonary lesion was well walled-off.

There is little reason to suppose that the calcifying pancreatitis is tuberculous in nature. In both of our patients the diabetes antedated the pulmonary tuberculosis by approximately two years, and in the first case steatorrhea definitely preceded the pulmonary lesion by about 18 months. Autopsy reports on cases of pancreatic calcification, even when complicated by pulmonary tuberculosis, do not mention (except for one case)<sup>2</sup> the finding of tuberculous lesions in the pancreas.

The treatment of chronic calcifying pancreatitis involves both medical and surgical procedures. Diabetes and steatorrhea are medical problems and the former needs no discussion here. Steatorrhea will usually respond to dietary measures and replacement therapy with pancreatic enzymes. A low fat diet is indicated, not only because these patients are often intolerant of fatty foods, but also because such a diet has been shown both experimentally and clinically to produce the greatest stimulation of pancreatic production of amylase and trypsin. Conversely, a high fat diet definitely suppresses secretion of pancreatic ferments. Pancreatin was moderately helpful in correcting the troublesome fatty diarrhea in the first case, and exerted no appreciable effect on the character of the stools of the second patient during the short time it was used. It should be stated, however, that the doses of pancreatin given to these two patients were woefully inadequate. To be effective in pancreatogenous diarrhea, 10 to 30 grams of pancreatin should be given daily.<sup>14</sup> The addition to the diet of protein-digests and amino acid preparations in which the work of pancreatic enzymes has already been done *in vitro* has recently added an important therapeutic measure to the management of this enzyme-deficiency state.<sup>14</sup> Because of the faulty absorption of vitamins, especially those of the fat-soluble group, the diet should be supplemented by massive doses of these substances.

Acute exacerbations of pancreatitis, whether interstitial or hemorrhagic in type, should be managed medically, according to a growing consensus. The pain, which varies in character and intensity depending on the nature of the underlying process, usually requires opiates but occasionally responds to ephedrin. Parenteral replacement of fluids lost by vomiting and diarrhea is essential, and the usual measures are employed to combat distention and shock when these occur.

Surgical intervention is clearly indicated when ductal stones are demonstrated, either alone or with parenchymal calcifications when there is reason to believe that pain or achylia will be relieved by the removal of the stones. Chronic obstruction of the duodenum calls for a short-circuiting operation such as gastroenterostomy, or for a partial pancreatectomy. Encroachment on the bile duct by the enlarged pancreas with the production of chronic, persistent pain is relieved by either internal biliary drainage (anastomosis of the

common duct to the stomach, duodenum, or jejunum), or external drainage by means of choledochostomy or cholecystostomy. Pain and pressure symptoms arising from pancreatic cysts which sometimes occur in chronic pancreatitis are relieved by marsupialization or internal drainage of the cysts into the small intestines. When intractable pancreatic pain is not demonstrably due to any of the above mentioned factors, more radical surgery may be necessary. Successful subtotal pancreatectomy with complete relief of pain in a small number of such patients has been reported during the past year.<sup>4, 19</sup>

### SUMMARY

1. Two cases of chronic pancreatitis with calcification, diabetes, and steatorrhea are reported.
2. Both cases were complicated by pulmonary tuberculosis.
3. The incidence, classification, pathogenesis, clinical features, and treatment of calcifying pancreatitis are briefly discussed.

### BIBLIOGRAPHY

1. PASCUCCI, L. M.: Pancreatic cyst and lithiasis, *Am. Jr. Roentgenol.*, 1944, lli, 80-87.
2. SNELL, A. M., and COMFORT, M. W.: The incidence and diagnosis of pancreatic lithiasis, *Am. Jr. Digest. Dis.*, 1941, viii, 237-243.
3. GRANEY, C. M., and REDDICK, R. H.: Calcification of the pancreas, *Am. Jr. Surg.*, 1944, lxxv, 271-275.
4. COMFORT, M. W., GAMBILL, E. E., and BAGGENSTOSS, A. H.: Chronic relapsing pancreatitis, *Gastroenterology*, 1946, vi, 239-285 and 376-408.
5. MARSHALL, W. A.: Pancreatic lithiasis, with case report and autopsy findings, *Radiology*, 1938, xxxi, 562-566.
6. FANGER, H.: Pancreatic lithiasis with associated intestinal hemorrhage, *New Eng. Jr. Med.*, 1944, ccxxxi, 678-680.
7. KALINOVSKY, L. B., and HOCH, P. H.: Shock treatments, 1946, Grune and Stratton, New York.
8. PASTERNAK, J. G.: Calcareous pancreatitis, *Ann. Int. Med.*, 1943, xix, 757-767.
9. BANTING, F. G., and BEST, C. H.: The internal secretion of the pancreas, *Jr. Lab. and Clin. Med.*, 1922, vii, 251-266.
10. BARRON, M.: The relation of the islets of Langerhans to diabetes with special reference to cases of pancreatic lithiasis, *Surg., Gynec. and Obst.*, 1920, xxxi, 437-448.
11. ELMAN, R.: Acute interstitial pancreatitis, *Surg., Gynec. and Obst.*, 1933, lvii, 291-309.
12. EDMONDSON, H. A., and FIELDS, I. A.: Relation of calcium and lipids to acute pancreatic necrosis, *Arch. Int. Med.*, 1942, lxxiv, 177-190.
13. ELMAN, R., and SACHAR, L. A.: Contributions made in 1940 to knowledge in regard to the pancreas, *Am. Jr. Digest. Dis.*, 1941, viii, 105-112.
14. ELMAN, R., and AKIN, J. T.: *Gastroenterology*, 1944, ii, 412-426.
15. CARTER, S. J.: Serum amylase findings in chronic alcoholic patients with acute, severe abdominal symptoms, *Ann. Surg.*, 1945, cxxii, 117-121.
16. WEINER, H. A., and TENNANT, R.: A statistical study of acute hemorrhagic pancreatitis, *Am. Jr. Med. Sci.*, 1938, cxcvi, 167-176.
17. MYERS, W. K., and KEEFER, C. S.: Acute pancreatic necrosis in acute and chronic alcoholism, *New Eng. Jr. Med.*, 1934, ccx, 1376-1380.
18. CLARK, E.: Pancreatitis in acute and chronic alcoholism, *Am. Jr. Digest. Dis.*, 1942, ix, 428-431.

19. NUZUM, F. R.: Diffuse calcification of the pancreas, *Jr. Am. Med. Assoc.*, 1943, cxxxii, 574-575.

DISCUSSION BY ALFRED S. HARTWELL, M. D.:

No paper on calcareous pancreatitis should fail to mention the interest with which for 40 years Dr. Joseph H. Pratt has studied pancreatitis. In recent years he has been interested in the secretin test of pancreatic function. He obtained from Ågren and Lagerlöf<sup>1</sup> some purified crystalline secretin and administered it intravenously to patients with actual, and also suspected, pancreatic disease. It will be recalled that secretin was first shown to exist by Bayliss and Starling<sup>2</sup> in 1902. This substance, which is extracted from small intestinal mucosa, when injected intravenously causes a very large volume of alkaline pancreatic juice to be excreted by the pancreas. When constant duodenal and gastric drainage is used, so that the gastric contents are kept separate from the duodenal contents, one can determine with considerable accuracy the volume of pancreatic juice which a given amount of secretin will cause to be excreted. The intubation of the duodenum and constant suction of it with controlled negative pressure is a time-consuming procedure and is largely restricted to centers where research is carried out. It would have been of interest, however, to have done secretin tests of pancreatic function in these two cases. The reader is referred to the discussion of pancreatic disease by Dr. Pratt in the Frank Billings Lecture of 1942.<sup>3</sup>

<sup>1</sup> ÅGREN, C., and LAGERLÖF, H.: The pancreatic secretion in man after intravenous administration of secretin, *Acta med. Scandinav.*, 1936, xc, 1.

<sup>2</sup> BAYLISS, W. M., and STARLING, E. H.: The mechanism of pancreatic secretion, *Jr. Physiol.*, 1902, xxviii, 325.

<sup>3</sup> PRATT, J. H.: Pancreatic disease, *Jr. Am. Med. Assoc.*, 1942, cxx, 175.

# A SURVEY OF THE ACTUALITIES AND POTENTIALITIES OF EXFOLIATIVE CYTOLOGY IN CANCER DIAGNOSIS \*

By GEORGE N. PAPANICOLAOU, M.D., *New York, N. Y.*

IN 1925, when for the first time I had occasion to discuss with the late Dr. James Ewing, then Professor of Pathology in our School at Cornell, the possibility of using the vaginal smear as an aid in the diagnosis of uterine cancer, he asked me whether this method could be applied to endometrial as well as to cervical carcinomas. It was his opinion that such a method might prove to be of greater value in the diagnosis of adenocarcinomas of the endometrium than in carcinomas of the cervix, for which everyone would most likely resort to the well established and more dependable method of biopsy.

At that time my knowledge of the cytologic method was very limited and I was in no position to state whether a differential diagnosis between carcinomas of the cervix and adenocarcinomas of the fundus on a cytologic basis was possible. Nor did I know then that the diagnosis of carcinomas of the cervix by the smear method would be possible at an early asymptomatic stage, making it useful in detecting unsuspected lesions, which might still be invisible.

Now that the method has been tested by general use over a number of years our knowledge has been advanced to a point where we are able to differentiate with a fair degree of accuracy between lesions affecting different parts of the female genital tract, as well as between various cell types and smear patterns. We are now in a position to make a clearer distinction between the squamous cell type carcinomas of the cervix and the adenocarcinomas of the endometrium, in which the abnormal cells are of the glandular type. It is even possible at times to make a differentiation between an adenocarcinoma of the endometrium and one of the cervix, in which the abnormal cells are of the endocervical type.

Metaplasias of the endocervix and of the endometrium may also be recognized occasionally when clusters of endocervical or endometrial cells are present, in which some of the cells show a change toward the parabasal squamous type. In metaplasia of the endometrium one often encounters rosette-like clusters of cells in which there is marked enlargement and vacuolization of some of the more peripherally located cells. Endocervical or endometrial polypoid hyperplasias may be revealed by small polypoid fragments of the endocervical or endometrial mucosa found in endocervical or endometrial smears.

\* Presented as a Morning Lecture, Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 30, 1949.

The original work referred to in this paper has been aided by the Commonwealth Fund and by the National Cancer Institute.

From Cornell University Medical College.

Ovarian carcinomas can be detected in the smears when there is metastasis to the tubes or the uterus. The cytology of metastatic cystadenocarcinomas of the ovary is usually sufficiently characteristic to permit their distinction from primary adenocarcinomas of the uterus.

Recently we had occasion to study two cases\* in which numerous cystadenocarcinoma cells were found in smears aspirated from the endometrial cavity,† whereas no such cells were found in the vaginal smear taken from one of the two cases. In neither of these was there any evidence of metastasis to either the uterus or the tubes. However, much ascitic fluid was present in both cases, and it is possible that such fluid, containing malignant cells, carried them through the tubes into the uterine cavity.

In cases of ovarian carcinomas with exudation of fluid into the peritoneal cavity malignant cells may be recovered in the centrifuged exudate.

Tubal carcinomas can be diagnosed by means of smears, but their origin cannot be well established unless fluid is drawn directly from the tube.‡

In the cervical carcinomas some distinctive smear patterns may be recognized.

In advanced squamous cell carcinomas of the cervix there is, as a rule, a great variety of atypical cells showing marked structural and nuclear abnormalities. Some of the cells acquire bizarre forms. Clusters of malignant cells are frequently encountered and show crowding, anisokaryosis, disorientation, engulfment and other abnormal features.

In carcinomas of the cervix which are still in an early intraepithelial stage the cytologic changes are less marked. The nuclei show distinct abnormal features such as enlargement, hyperchromasia, anisokaryosis, bi- or multinucleation, etc., but the malignant cells do not exhibit the extreme deviations from the normal types from which they originate, as they do in advanced cases of malignancy. Furthermore, in the early carcinomas the malignant cells usually appear singly or in small groups in contrast to advanced carcinomas, in which larger and more crowded groups are present.

\* These cases were referred to us by Dr. Sophia Kleegman.

† The method of aspiration is described by Dr. Kleegman as follows:

The vagina and cervix are cleansed with Tincture of Merthiolate and the anterior lip of the cervix grasped with a tenaculum. An antrum cannula attached to an empty, closed 5 c.c. syringe is then inserted directly into the endometrial cavity, approximately .5 inch from the fundus. If the internal os is very tight, it may be necessary to pass a number 9 or number 10 Hank dilator through the internal os. Usually, dilatation is not necessary. With the antrum cannula in the endometrial cavity, the plunger of the syringe is withdrawn, creating suction. The syringe is then detached from the cannula, closed, and again attached, suction is applied for a second and then a third time. This will give sufficient material to make an adequate examination. The cannula is then withdrawn from the uterus, and the contents are expelled on the end of a glass slide by blowing air through the cannula. The material is spread over the lower inch of the slide, and dropped promptly into the alcohol-ether solution. Not infrequently, a small strip of endometrium will also be aspirated in this way, comparable to the amount of material obtained with an endometrial biopsy curet. If desired, this can be fixed and prepared for a pathological examination.

‡ Thus far we have had only one case, referred to us by Dr. Virginia Pierce of Memorial Hospital, in which fluid was obtained from each one of the tubes separately. A pre-operative diagnosis of carcinoma of the left tube was made possible in this case by the cytologic examination of the two specimens.

The term "dyskaryosis" has been adopted to designate these early cytologic changes, which are centered in the nucleus. Several types of dyskaryosis may be distinguished on the basis of a predominance of one or more distinctive cell types.

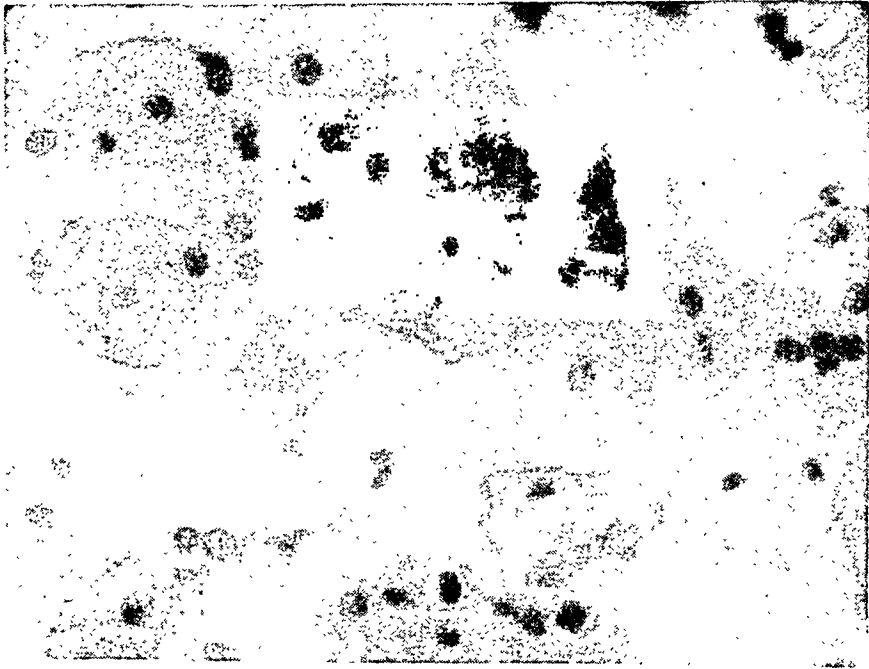


FIG. 1, a. Superficial squamous cells. Normal.  $\times 400$ .

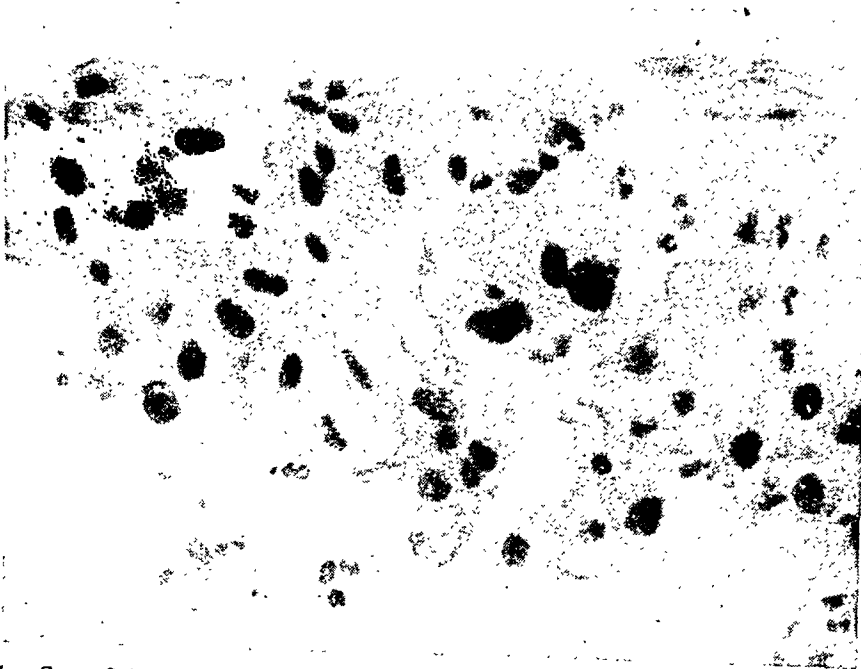


FIG. 1, b. Superficial squamous cells characteristic of superficial cell dyskaryosis.  $\times 400$ .

We speak of a "superficial cell dyskaryosis"<sup>1</sup> when the prevailing abnormal cells are of the superficial squamous type (figures 1a, 1b). Some of these abnormal cells may be cornified and, as a rule, a relatively high degree of cornification is associated with this condition, which is the most commonly met with of all the forms of dyskaryosis.

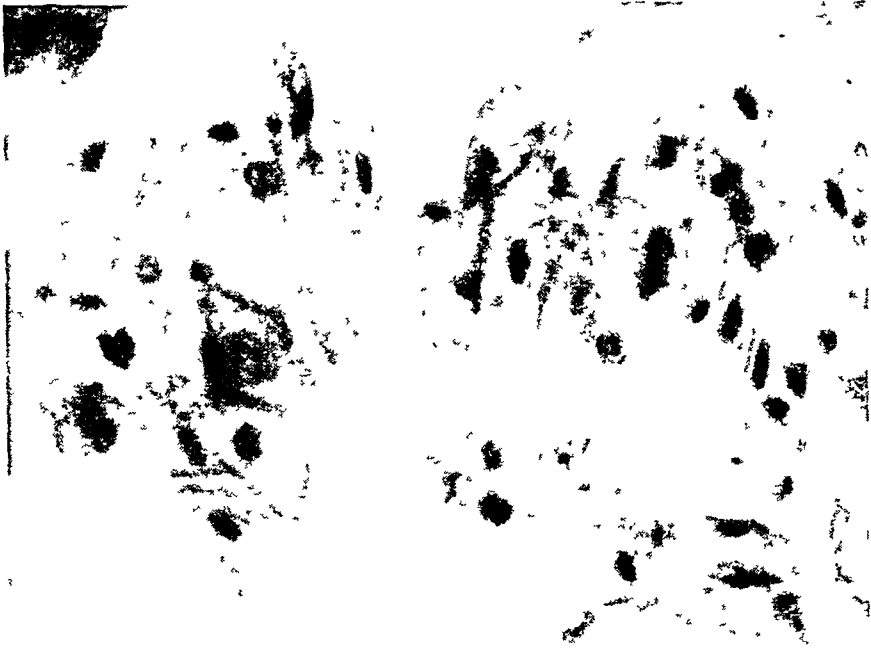


FIG 2, a. Intermediate (navicular) cells. Normal.  $\times 400$ .

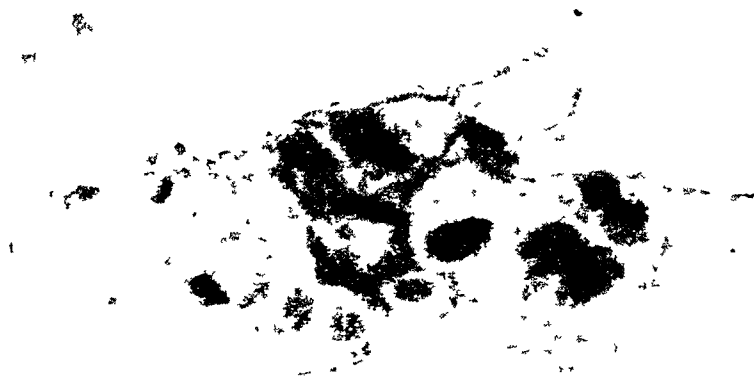


FIG 2, b. Intermediate (navicular) cells characteristic of intermediate cell dyskaryosis  $\times 400$

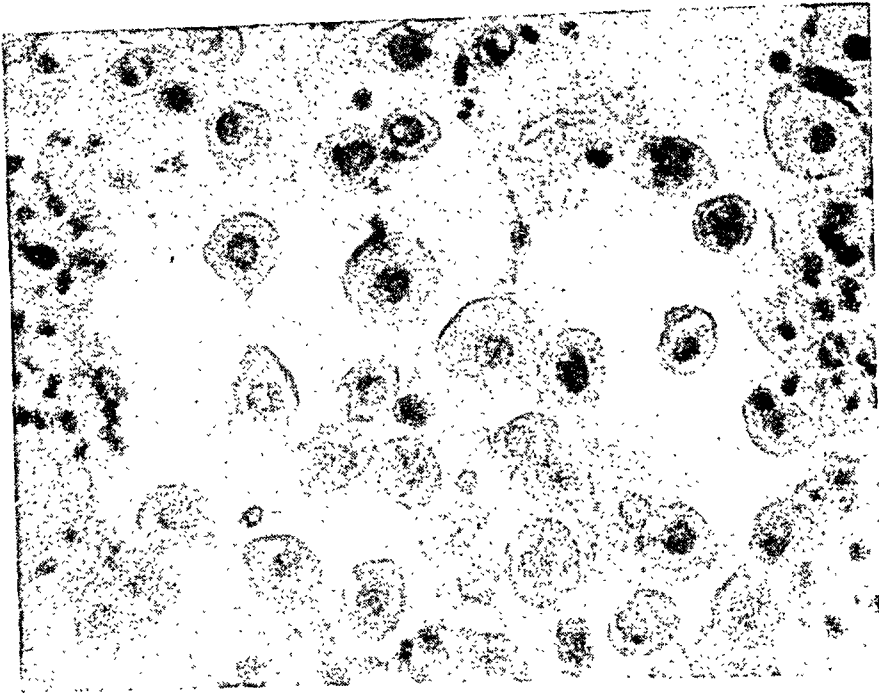


FIG. 3, *a*. Cervical parabasal cells. Normal.  $\times 400$ .

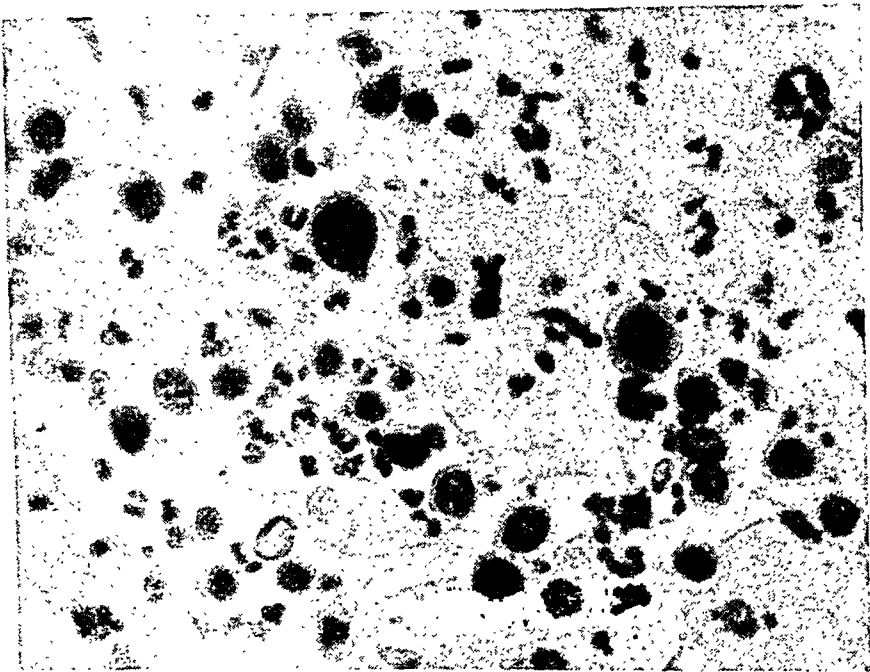


FIG. 3, *b*. Cervical parabasal cells characteristic of parabasal cell dyskaryosis.  $\times 400$ .

The term "intermediate or navicular cell dyskaryosis" is used to indicate the prevalence of abnormal cells deriving from the intermediate or navicular zone (figures 2a, 2b). This type of dyskaryosis is rather rare and thus far we have had only two clear-cut cases of it.



A third type, the "parabasal cell dyskaryosis", is characterized by a preponderance of abnormal parabasal cells (figures 3a, 3b).

Still another type of dyskaryosis is that in which the prevailing abnormal cells are of endocervical origin (figures 4a, 4b).

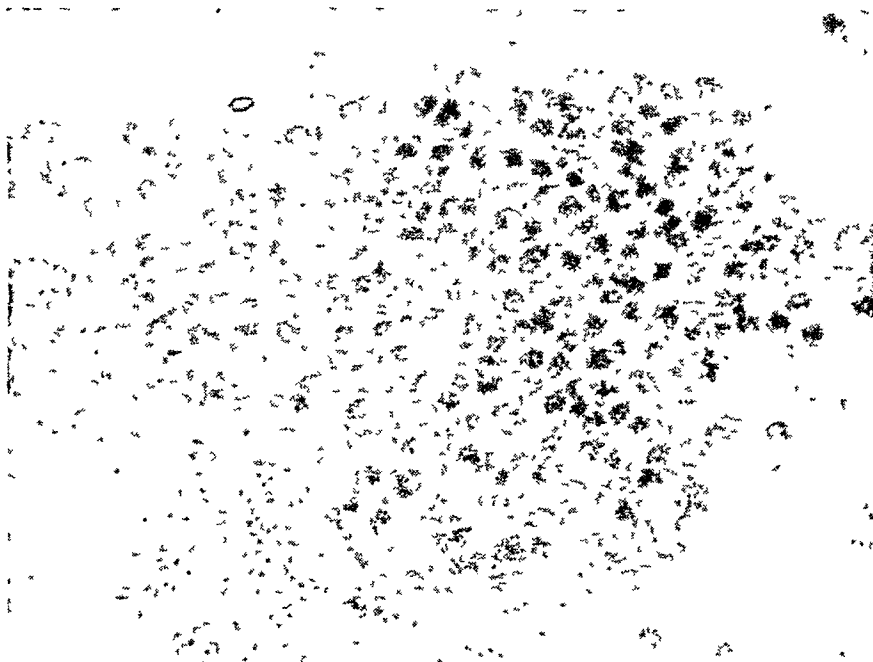


FIG 4, a. Endocervical cells. Normal.  $\times 400$

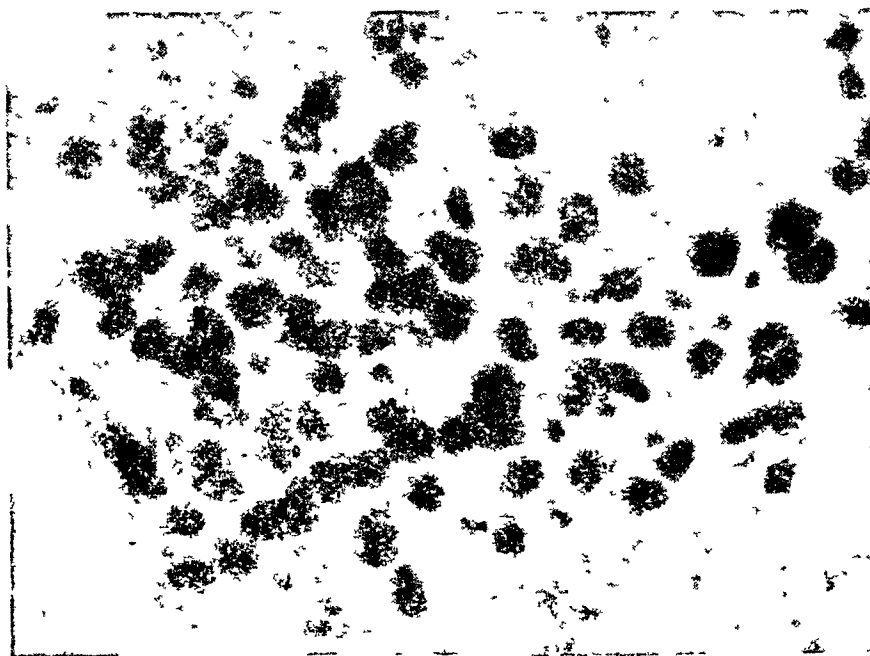


FIG. 4, b Endocervical cells characteristic of endocervical cell dyskaryosis.  $\times 400$

The significance and the prognostic value of these different patterns which seem to correspond to the earliest stages of malignant lesions of the cervix are not yet properly understood, nor will they be until an exhaustive correlative study of cytologic and pathologic findings has been made. What tends to complicate the picture is that not infrequently cells representing various dyskaryosis types are found to be intermixed.

Cases have also been noted in which the dyskaryotic cytology was found to coexist with that of an invasive squamous cell carcinoma. In some of these cases transitional cell forms linking the two cytologic patterns have also been observed. Should this fact be interpreted as indicating that the one would eventually develop into the other? An affirmative answer would be only an assumption, since in none of these cases have we had any positive evidence of a progressive change from one pattern to the other. On the other hand, in at least one case of superficial cell dyskaryosis, which we followed over a period of 10 years, this condition proved to be reversible.

Our observations in this field of early malignant lesions of the cervix and of their corresponding cytologic patterns are still fragmentary. It is not always possible to obtain a confirmation of smear findings by biopsy. Instances are not uncommon in which multiple biopsies have been necessary to prove the presence of an early carcinoma. In a recent case, only one out of eight biopsies taken offered positive evidence of a carcinoma in situ. Even after complete hysterectomy it is not possible to verify the absence of a malignant lesion without a serial microscopic study of the cervix, which is impracticable as a routine procedure.

Another difficulty is the lack of general agreement among pathologists as to the criteria of a carcinoma in situ. It sometimes happens that a section showing a marked degree of epidermidalization may be interpreted in some laboratories as carcinoma in situ. All these reasons make it very difficult to evaluate accurately the incidence of carcinoma in cases in which a dyskaryosis smear pattern has been observed.

In view of the fact that at present no general agreement can be reached as to the criteria of carcinomas in situ, their separation into two groups appears to be justifiable. One of the two groups would include cases characterized by clean-cut criteria that would be generally acceptable and that would satisfy the most exacting standards; the other would consist of cases in which the criteria fall below such standards and in which there may be disagreement as to the true nature of the lesion.

The term "carcinoma in situ" or "intraepithelial carcinoma" should be retained for the first group, whereas the second one should be designated by a new term which would not necessarily suggest malignancy. The term "pre-cancerous", which has been used extensively for ambiguous lesions, would be rather objectionable, as it implies an inevitable malignant transformation. In a recent discussion of this point the term "dysplasia" \* was

\* This term was suggested by Dr. William B. Ober of the National Cancer Institute at Bethesda, Maryland.

proposed to specify such cytologic changes as would be suggestive of but not conclusive for malignancy.

The acceptance of a new term to designate a distinct group which would include all cases that are questionable or apt to be contested from the pathological standpoint would greatly contribute to a more satisfactory and less controversial evaluation of early malignant lesions. Moreover, the term "dysplasia", like that of dyskaryosis, may be advantageously combined with other terms specifying the site of the lesion and the predominating cell type, thus adding greatly to its descriptive value.

In the early period of our studies only vaginal aspiration smears were used. We now consider the vaginal smear alone rather inadequate, and in addition to it, we request an endocervical aspiration smear and a direct cotton swab or spatula smear. In cases in which an adenocarcinoma of the fundus or a carcinoma of the ovary is suspected, an endometrial aspiration smear is of great value.

In some laboratories only a swab or spatula smear is used. Our experience is that with such a limitation one may often miss carcinomas of the uterine fundus, of the tubes and of the ovaries, or even of the cervix, if the site of the malignant lesion happens to be outside the area covered by the swab or spatula.

Our technical procedures related to fixation and staining are now fairly well standardized. We still adhere to the principle of an immediate fixation in alcohol-ether and of an adequate staining technic which brings out the nuclear structure, and insures transparency of the cytoplasm and a good differentiation between the basophilic and acidophilic cells.

With regard to the use of the smear technic in the diagnosis of malignant neoplasms of organs other than those of the female genital tract, it appears that a higher level of standardization and accuracy has been achieved in the diagnosis of carcinomas of the respiratory tract, by the cytologic examination of sputum and of bronchial aspirates and washings. This is a field in which considerable progress has been made through the work of previous investigators. By using cytologic criteria we now feel that it is possible not only to detect the presence of carcinoma in the lungs, but also to recognize a number of distinct types.

The squamous cell type is probably the one presenting the most characteristic cytologic picture. The presence of cells showing squamous metaplasia and a strong acidophilic, or rather, orangeophilic reaction, in association with marked nuclear abnormalities, helps toward an easier and safer recognition of neoplasms of this type.

In undifferentiated bronchogenic carcinomas the malignant cells appear in clusters showing an irregular pattern and nuclear abnormalities such as enlargement, anisokaryosis, prominence of the chromatin and of the nucleoli, and other changes characteristic of malignancy.

Carcinomas of the oat celled type can be surely identified by the small size

of the malignant cells, their extreme hyperchromasia, the anisokaryosis and the scantiness of the cytoplasm.

Adenocarcinomas may be recognized as such when the cells are well preserved and reveal their glandular origin. Exfoliated cells of this type frequently show an eccentric position of the nucleus and vacuolization of the cytoplasm. The cells are often grouped in rosette-like clusters.

Malignant neoplasms of lymphoid origin, such as Hodgkin's disease or reticulum-cell sarcoma, also present a distinct cytologic picture. The cells appear, as a rule, singly, and although relatively small, they can be safely identified by the coarse granulation, hyperchromasia, and fragmentation of their nuclei. An excess of lymphocytes was observed in some cases of lymphatic leukemia. In general, it may be stated that large clusters of lymphocytic cells in sputum or bronchial washings appear to be almost invariably associated with malignant neoplasms.

Another group of neoplasms of the lungs which show good exfoliation and can be detected by the examination of sputum or bronchial washings is that of the alveolar cell carcinomas. A cytologic feature which may help in the recognition of this type is the not infrequent presence of multinucleated cells of a rather characteristic appearance.

Of the non-malignant conditions, one which may occasionally display a distinctive cytology is bronchiectasis. Clusters of atypical cells which are sometimes found in this condition show considerable resemblance to clusters of neoplastic cells. The normal structure and the uniformity of their nuclei are a help in interpreting them correctly.

In our laboratory we attribute equal importance to the examination of sputum and to that of bronchial aspirates and washings. We have had instances of positive cases in which the sputum was negative and the bronchial washing positive, but other cases in which the contrary was true. When findings are negative at least three specimens should be examined.

In order to secure a good preservation of the cells we fix the sputum specimens in 70 per cent alcohol as soon as collected. The bronchial washings are mixed immediately with 95 per cent alcohol and then centrifuged. Smears prepared from the sputum, as well as those prepared from the sediment of the bronchial washings, are fixed again in alcohol-ether and stained by our standard smear-staining procedure which insures a good differentiation between basophilic and acidophilic cells. This differentiation is most important for the detection of the acidophilic and orangeophilic cells which are a characteristic feature of the squamous cell carcinomas.

In the urinary tract the most successful application has been in carcinomas of the bladder. As a rule, carcinomas of this organ exfoliate copiously and the cells usually appear in clusters showing structural abnormalities which reveal their malignant nature. In two instances an unsuspected carcinoma, concealed in a diverticulum of the bladder, has been detected by the use of the smear technic.

Papillomas also exfoliate profusely and show great variation in their cytologic picture. Some throw off normal cells, the most characteristic of which are those having a columnar form, others shed abnormal cells with distinct, malignant features, while in an intermediate group the exfoliated cells show an admixture of normal and abnormal types. Cytologic findings may thus be of value in determining the benign or malignant nature of a papilloma. We have repeatedly had cases in which the diagnosis of a malignant papilloma was established by the smear method. In one of these, in which the smear report was positive, a first biopsy was interpreted as negative, and it was only by a second biopsy performed 13 months later that the malignant nature of the tumor was confirmed.

In prostatic carcinomas our progress has been rather slow, due to the fact that for a long time only voided urine specimens were sent to us for examination. The chances of finding prostatic cells in such specimens are rather small. We now require three specimens, one of a prostatic secretion and two of voided urine, one obtained before and one after a prostatic massage. With such specimens the probability of recovering carcinoma cells is greatly enhanced. However, our knowledge of the normal and malignant cytology of the prostate is still incomplete, and there are several cell types, the nature of which can not yet be satisfactorily interpreted.

In some of the prostatic carcinomas the exfoliated cells and their nuclei display very pronounced malignant characteristics. In others the cells are relatively small and of rather uniform structure, making more difficult the recognition of their malignant nature. There is good reason to believe that with increased cytologic knowledge and with the availability of more adequate specimens the smear method in the diagnosis of prostatic neoplasms will reach a much higher level of standardization and accuracy.

Neoplasms of the ureters and of the pelvis of the kidney usually show good exfoliation, as do those of the bladder. In several instances the diagnosis of malignancy has been established chiefly by the cytologic examination of urine sediment. In one case, in which an operation was performed almost exclusively on the strength of repeated positive smear findings, a very early carcinoma of the pelvis was found.

Exfoliated cells deriving from the pelvis of the kidney may be recovered in catheterized bladder, or even in voided, urine, but they appear in much larger numbers in ureteral specimens. Unfortunately such ureteral specimens show marked variability in their cytologic picture, which is apt to lead to misinterpretation. Bi- or multinucleated cells, or cells with greatly enlarged nuclei, are quite frequently encountered. There have been instances in which as many as 60 or 80 nuclei have been noted in a single cell. However, the nuclei of all these atypical cells retain their normal structure and do not show the extreme aberrations which are found in the nuclei of malignant cells.

Carcinomas of the kidney show a considerable variability in their exfoliation. In some instances the exfoliation is so profuse that malignant cells are found in large numbers in a voided urine specimen, whereas in others it is

very scanty. The specific cytology of various types of tumors of the kidney still needs further clarification. Special methods of staining may eventually be found to be necessary for the identification of some of these types.

The administration of estrogens causes marked changes in the epithelium of some of the organs of the urinary tract. As a rule, these changes are reflected in the smears.- Both the transitional epithelium of the bladder and the glandular epithelium of the prostate may show cellular and nuclear enlargement and an increased production of glycogen as the result of a prolonged estrogenic therapy. Some of the superficial transitional cells change to a type resembling that of the cornified small-nucleated acidophilic squamous cells found in the vaginal secretion.

It is of interest that a prolonged administration of estrogens in prostatic carcinomas may cause an enlargement not only of the normal but also of the cancer cells, thus greatly facilitating their recognition in the smears. It is, therefore, likely that the use of estrogen therapy prior to the smear examination will tend to increase exfoliation and to cause cytologic changes that would help in the identification of exfoliated cancer cells. Such a use of estrogens has been proved to be of value in carcinomas of the female genital organs.

With regard to the matter of obtaining suitable urine specimens it may be stated in general that catheterized specimens are preferable to voided, more necessarily in women because of the admixture of vaginal cells in voided urine. The types of urine specimens required for the diagnosis of lesions of the prostate or of the ureter and kidney have already been mentioned.

The urine is mixed with an equal amount of 95 per cent alcohol as soon as collected.\* It is subsequently centrifuged, and smears prepared from the sediment are fixed again in an alcohol-ether solution and then stained by the same method used for other smears.

Special difficulties are encountered in the use of the smear method for the diagnosis of gastric carcinomas. Of these the two most important are the relatively rapid deterioration of exfoliated cells in the gastric fluid and the continual emptying of the gastric contents into the intestines, which does not allow a sufficiently large accumulation of exfoliated cells within the stomach. Another adverse factor is the rather frequent presence of extraneous cells in the gastric fluid. Clusters of cells from the nasal and bronchial mucosa and dust cells are those apt to be the most troublesome.

Despite these drawbacks the cytologic method is of recognized value in the diagnosis of gastric carcinomas. By improving our cytologic criteria and our technical procedures we hope to bring this application up to much higher standards, although the percentage of false negatives will most likely remain higher in this than in other applications.

\* The procedure of fixing specimens immediately and prior to centrifugation by mixing them with equal amounts of 95 per cent alcohol applies to all fluids with the exception of pleural and peritoneal fluids. These are mixed with equal amounts of 50 per cent alcohol, as the 95 per cent alcohol causes a much greater coagulation of proteins, which tends to reduce the amount of sediment.

Fluid aspirated from the duodenum is mostly acellular and, as a rule, it offers very little in the way of positive information. There are, however, cases which demonstrate its occasional value, such as one that we had of carcinoma of the pancreas, in which a positive diagnosis was established by the recovery of cancer cells in the duodenal drainage.<sup>2</sup>

For the gastric application, aspirates as well as washings may be used. Saline washings prove to be the most satisfactory. Gastric specimens should be centrifuged and smears prepared from the sediment without delay in order to insure a good preservation of the cells.

The difficulty in obtaining good specimens from the lower bowel, free from fecal contamination, has been the main reason why the cytologic study of specimens of this type has not, up to now, been given the attention which it actually deserves. Recent technical improvements have put this application on a more practical basis. A cathartic followed by a hot soap enema the next morning generally clears the lower part of the intestine sufficiently to make it possible to obtain a clean saline washing.

Smears prepared from the centrifuged specimens of such rectal washings show good cellular preservation. The relatively uniform cytology of smears of this type greatly facilitates the recognition of malignant cells.

Normal cells from benign rectal polyps can be easily identified by their columnar form. Their nuclear structure remains normal and contrasts with that of the abnormal nuclei found in adenocarcinomas of the rectum. Whenever a lesion is visible, a direct smear is a valuable supplement.

The cytologic technic is also successfully applied to the pleural and peritoneal fluids. The cytology of these fluids is relatively simple, yet we often find it difficult to differentiate accurately between cancer cells and atypical mesothelial cells or histiocytes, which are frequently present in these fluids. In this application a special staining technic permitting a safer identification of the histiocytic elements would be of great value.

Malignant neoplasms of other parts of the body may be diagnosed by the use of the same technic. Carcinomas of the esophagus may be detected through the cytologic examination of esophageal and gastric aspirates and sometimes of sputum. Laryngeal carcinomas can be diagnosed by sputum or by scraping or swab smears. Carcinomas of both the esophagus and the larynx shed copiously. Cells of carcinomas of the gall bladder may be found in fluid aspirated from that organ. Antrum carcinomas may be detected by the examination of washings. Cystic growths may be explored by aspiration. Breast tumors often yield a sufficient amount of secretion to make their diagnosis possible. Tumors of the skin or of the oral cavity may be identified by the examination of scrapings.

Some of these applications have hardly been touched thus far. It will take many years before they have been fully explored and before their comparative cytology has been thoroughly scrutinized. In attempting to evaluate this method we should therefore take into consideration not only its actual status but its future potentialities as well.

As far as actual results are concerned it may be safely stated that certain applications, such as those of the female genital tract and of the respiratory tract, have been advanced to a point where they can now be used in routine laboratory diagnosis. There is an increasing number of publications dealing with the practical advantages and disadvantages of the method and giving an estimate of its dependability as a diagnostic procedure. Although the results obtained by investigators in different laboratories are at variance in some respects, they do permit one to arrive at certain conclusions, in which there is more or less general agreement.

One important point on which there is evidence of such an agreement is that the cytologic method is not to be considered as a method of final diagnosis and that confirmation of smear findings by biopsy or curettage is indicated wherever possible.

On the other hand, it is generally conceded, even by those who are most skeptically inclined, that this method is of unquestionable value in the detection of early or unsuspected carcinomas of certain organs, and is, therefore, particularly adapted to screening purposes. It is also highly useful in evaluating the effects and in following up the results of irradiation or other therapy.

With regard to the diagnostic accuracy of the method, it would be very difficult to make an overall statistical evaluation which would apply to all groups. Figures given out by various investigators show considerable variation. What we are striving for in our laboratory is to limit to a minimum the percentage of false positives. We feel that an accuracy of over 95 per cent can and should be maintained in the cases reported as Class IV and of over 98 per cent in those reported as Class V.\* Anything below these figures would not be at all satisfactory, more particularly in the Class V group, in which reports are often used as the basis of a decision for a major operation. Negative reports, as a rule, show a higher percentage of errors, ranging from 5 or 10 per cent, in well explored gynecological cases, to 25 per cent or even more in other applications, more specifically in the gastric.

Some of the drawbacks of the cytologic method are that it is time consuming and that it requires special study even on the part of men with a good pathological background. These disadvantages constitute a serious obstacle to the incorporation of the method in many laboratories and will, no doubt, greatly retard its more widespread adoption. What is more discouraging is the fact that in some laboratories, because of an increasing demand, the method is introduced prematurely, and is put into practice by men who have

\* Classification of reports on smears as applied to the diagnosis of malignant neoplasms

Class		
I	Negative	Absence of atypical or abnormal cells
II	Negative	Atypical cells present but without abnormal features
III	Suspicious	Cells with abnormal features suggestive of but not conclusive for malignancy
IV	Positive	Cells and cell clusters fairly conclusive for malignancy
V	Positive	Cells and cell clusters conclusive for malignancy



not had sufficient training. This does considerable harm and tends to discredit the method.

Should one attempt to evaluate the cytologic method and its general significance, he should bear in mind that it is still going through a period of evolution, and that our present achievements do not actually represent our maximum expectations in this new field. There is no doubt that the method possesses great potentialities, not only with regard to its practical usefulness in cancer diagnosis, but also in its more fundamental value as a new branch of the morphological sciences. Judging from the progress that has been made during the last few years we can look forward with confidence to higher future accomplishments. However, many more years of arduous work lie ahead of us if we are to explore this wide new field and to derive all the benefits which might be expected from it.

#### BIBLIOGRAPHY

1. PAPANICOLAOU, GEORGE N.: Cytologic diagnosis of uterine cancer by examination of vaginal and uterine secretions, *Am. Jr. Clin. Path.*, 1949, xix.
2. McNEER, GORDON and EWING, JAMES H.: Exfoliated pancreatic cancer cells in duodenal drainage: a case report, *Cancer*, July 1949.

# CASE REPORTS

---

## ELECTROCARDIOGRAPHIC CHANGES IN A CASE OF WERNICKE'S SYNDROME \*

By LEON WALLACE, M.D., *Beverly Hills, California*, and  
EUGENE CLARK, M.D., *New York, N. Y.*

It is well known that the heart may be involved and that electrocardiographic changes are found in conditions due to deficiency of the vitamin B complex. This has been shown to occur in beriberi and pellagra.<sup>1, 2, 3, 4, 5, 6, 7, 8</sup> The following case is of interest because of the occult cardiac involvement with striking electrocardiographic abnormalities, which disappeared rapidly after thiamine chloride therapy, in a patient with Wernicke's syndrome (hemorrhagic polioencephalitis superior), a state which clinical and experimental evidence holds ascribable to thiamine deficiency.<sup>9, 10, 11, 12</sup>

### CASE REPORT

A 40 year old white man entered the hospital in a confused state. He was disoriented as to time and place, confabulated, and frequently contradictory. The only history which appeared to be reliable was the admission of chronic alcoholism for at least six years, accompanied by a grossly inadequate food intake. Diplopia of 24 hours' duration was admitted to be present; headache was denied. A questionable history of peptic ulcer was given. No history of heart disease was obtained.

At the time of admission the following physical findings were present: Temperature 99.2° F., pulse 150, respirations 20, blood pressure 114 mm. Hg systolic and 80 mm. diastolic.

The head showed no evidence of injury. The pupils reacted to light and accommodation, and were round, regular and equal. There was left external rectus palsy with diplopia; horizontal, but no vertical nystagmus. The fundi were normal. The ears, nose, mouth, throat and neck were essentially normal.

The lungs were clear to auscultation and percussion. The heart was not enlarged. The sounds were of good quality and regular. Sinus tachycardia was present. There were no murmurs or thrills.

The abdomen was flat and slightly tender in the right upper quadrant. The kidney, spleen and liver were not palpable. Genitalia were normal. The extremities revealed slight cyanosis of both feet and hands.

*Neurological examination:* Deep tendon reflexes were normal in the upper extremities, absent in the lower extremities. The Babinski reaction was equivocal, and plantar hyperesthesia was present.

*Laboratory findings:* White blood count 4850; neutrophils 60 per cent, lymphocytes 33 per cent, mononuclears 2 per cent, eosinophiles 2 per cent, basophiles 3 per cent. Red blood count 4,870,000; hemoglobin 14.5 gm. The Wassermann reaction was negative. Sodium: 312 mg./100 c.c. Non-protein nitrogen: 32 mg./100 c.c.

\* Received for publication November 15, 1946.

From the Third (New York University) Medical Division of Bellevue Hospital, and the Department of Medicine of the New York University College of Medicine.

Fasting blood sugar: 87 mg./100 c.c. Erythrocytic sedimentation rate: 26 mm. corrected (normal 0-10). Blood culture: negative. Urine: no abnormalities.

On admission, the diagnosis of Wernicke's syndrome was made. The patient was given 50 mg. of thiamine chloride intramuscularly at 11:00 a.m., and 50 mg. intravenously at 2:00 p.m. The strabismus and diplopia were gone at 4:00 p.m. Thereafter, 50 mg. of thiamine chloride were given daily.

The chest roentgenogram taken on admission was suggestive of tuberculosis. This was confirmed by the finding of acid-fast bacilli in the sputum. Repeated chest roentgenograms were reported as showing a mottled infiltration of the right apex of the lung with a small cavity above the first rib, together with an area of round infiltration 1.5 cm. in diameter in the second left intercostal space. Except for a fever which fluctuated between 100° F. and 103° F. for four days following admission the patient has been afebrile.

The electrocardiograms illustrated were taken on the day of entry, the following day, six days following admission, and 20 days following admission.

The abnormal ST-T complexes in Leads II and III which were seen on the first two days are shown to have reverted to normal by the sixth day.

Subsequent laboratory work performed two weeks following admission revealed: icteric index 5; total protein 8.2; albumin 4.74; globulin 3.46; cholesterol 153.6; cholesterol esters 129.9. The repeated neurological examination revealed the following: a persistence of the nystagmus, slight tenderness in the calf muscles, plantar hyperesthesia, and absent deep tendon reflexes in the lower extremities, normal plantar reflexes. At that time, a moderate adiadokokinesis was noted in the right arm; the muscle strength throughout was normal. The patient walked with a wide gait and lost his balance making quick turns to either side.

The final diagnosis was Wernicke's syndrome and pulmonary tuberculosis.

## DISCUSSION

The case herein reported is identified as that of Wernicke's syndrome (hemorrhagic polioencephalitis superior) by the presence of all of the essential features of the disease. The combination of an ophthalmoplegia promptly subsiding after thiamine therapy, with clouding of consciousness, ataxia, other signs of vitamin deficiency (i.e., peripheral polyneuritis), and a dietary history of inadequate thiamine intake, serves to establish the diagnosis.

Though there is nothing specific about the pattern of the electrocardiographic abnormalities which this patient showed, that they were an integral feature of his vitamin deficiency state is indicated by the absence of any clinical evidence of a structural cardiac lesion, by their similarity to electrocardiographic abnormalities previously reported in some cases of beriberi and pellagra,<sup>1, 2, 5</sup> and by the restitution of the electrocardiogram to normal within six days after thiamine therapy was begun. The electrocardiographic abnormalities cannot be ascribed to tachycardia since the ventricular rate 20 days following admission was approximately the same as that on the second day after admission although the electrocardiogram had long since become normal. No digitalis was given.

This case report is of special interest because the patient presented the clinical syndrome of Wernicke which has been ascribed to thiamine deficiency and at the same time presented occult cardiac involvement with marked electrocardiographic abnormalities. This case calls further attention to cardiac involvement associated with vitamin deficiency states and its apparent reversibility following adequate therapy. Routine electrocardiograms in these conditions may reveal

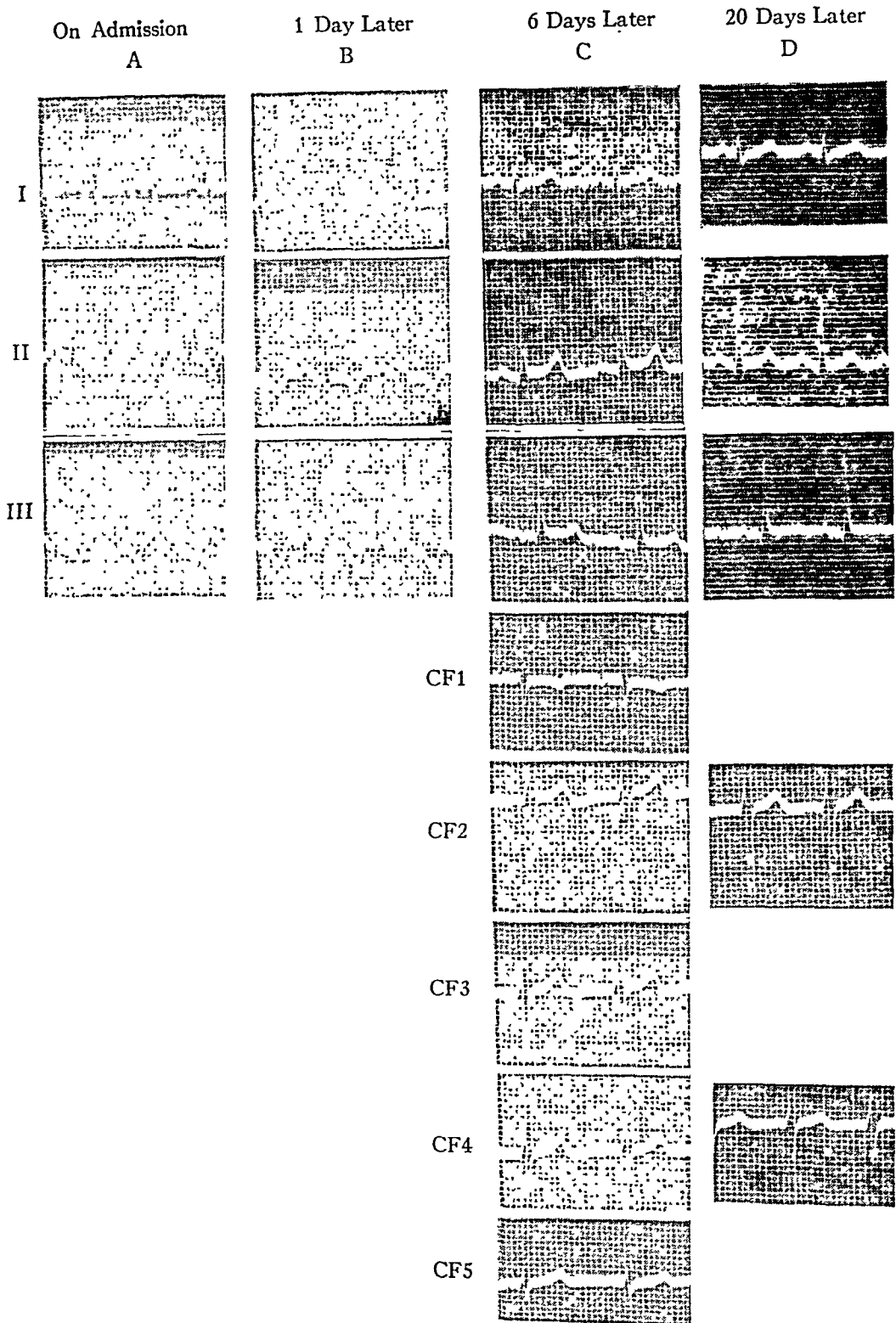


FIG. 1. *A.* On day of admission. Sinus tachycardia of 140. The abnormalities are the low T in Lead I and the inverted T in Leads II and III. *B.* One day later. Sinus tachycardia of 107. The low T in Lead I and the inverted T in Leads II and III persist. *C.* Six days later. Sinus rhythm of 83. The abnormal T waves are now normal as is the entire record. *D.* Twenty days later. Sinus tachycardia of 107. Normal record. The timer was not working while the first three leads were taken.

cardiac involvement before clinical manifestations are present and thereby be of value to the clinician.

### CONCLUSION

A case of Wernicke's syndrome is presented in which occult cardiac involvement with striking electrocardiographic abnormalities was found. Following intensive thiamine chloride therapy, these abnormalities were no longer present.

We are indebted to Dr. L. N. Katz for reading this paper and making suggestions.

### BIBLIOGRAPHY

1. FEIL, H.: A clinical study of the electrocardiogram and of the phases of cardiac systole in pellagra, *Am. Heart Jr.*, 1936, xi, 173-184.
2. WEISS, S., and WILKINS, R. W.: The nature of the cardiovascular disturbances in nutrition deficiency states (beri-beri), *Ann. Int. Med.*, 1937, xi, 104-148.
3. DUSTIN, C. C., WEYLER, H., and ROBERTS, C. P.: Electrocardiographic changes in vitamin B<sub>1</sub> deficiency, *New Eng. Jr. Med.*, 1939, ccxx, 15-21.
4. JOLLIFFE, N., GOODHART, R., GENNIS, J., and CLINE, J. K.: The experimental production of vitamin B<sub>1</sub> deficiency in normal subjects. The dependence of the urinary excretion of thiamin on dietary intake of vitamin B<sub>1</sub>, *Am. Jr. Med. Sci.*, 1939, cxviii, 198-211.
5. CAMPBELL, S. B. B., and ALLISON, R. S.: Pellagra, polyneuritis, and beri-beri heart, *Lancet*, 1940, i, 738-739.
6. MAINZER, F., and KRAUSE, M.: The electrocardiogram in pellagra, *Brit. Heart Jr.*, 1940, ii, 85-96.
7. GOLDFARB, W., and BOWMAN, K. M.: The vitamin B<sub>1</sub> requirement during insulin shock therapy, *Am. Jr. Psychiat.*, 1941, xcvi, 393-396.
8. RACHMILEWITZ, M., and BRAUN, K.: The presence of electrocardiographic changes in nicotinic acid deficiency and their elimination by nicotinic acid, *Am. Heart Jr.*, 1944, xxvii, 203-208.
9. WORTIS, H., BUEBING, E., STEIN, M. H., and JOLLIFFE, N.: Pyruvic acid studies in the Wernicke syndrome, *Arch. Neurol. and Psychiat.*, 1942, xlvii, 215-222.
10. ZIMMERMAN, H. M.: The pathology of the nervous system in vitamin deficiencies, *Yale Jr. Biol. and Med.*, 1939, xii, 23-28.
11. ALEXANDER, L.: Wernicke's disease, *Am. Jr. Path.*, 1940, xvi, 61-70.
12. EVANS, C. A., CARLSON, W. E., and GREEN, R. G.: Pathology of Chastek paralysis in foxes; counterpart of Wernicke's hemorrhagic polioencephalitis of man, *Am. Jr. Path.*, 1942, xviii, 79-91.

## AUREOMYCIN IN ACUTE INFECTIOUS MONONUCLEOSIS\*

By B. J. GRUSKIN, *New York, N. Y.*

SINCE the discovery of aureomycin,<sup>1</sup> an antibiotic obtained from a mold of the *Streptomyces* group, *Streptomyces aureofaciens*, investigation has shown it to be extremely effective both in vitro and in vivo against rickettsial organisms of several varieties as well as against certain viruses<sup>2</sup> and bacteria.<sup>3, 4</sup> Several reports have appeared during recent months indicating a singularly striking effectiveness against lymphogranuloma venereum,<sup>5</sup> brucellosis,<sup>6</sup> primary atypical pneumonia<sup>7</sup> and various types of ocular infections.<sup>8</sup> No report, to my knowl-

\* Received for publication March 28, 1949.

edge, has as yet appeared in the literature concerning its use in acute infectious mononucleosis. Because of the highly favorable results obtained with it in some viral diseases, it was deemed advisable to try aureomycin\* in a patient with this disease.

#### CASE REPORT

A white female, age 17, became ill on December 29, 1948 with malaise and slight fever. On the following day, she developed a sore throat and when she was first seen at her home on December 31, her temperature was 102° F. Examination at that time revealed the presence of a yellowish-white exudate on both faucial tonsillar stubs as well as on discrete lymphoid tissue deposits on each postero-lateral pharyngeal wall. The exudate assumed a follicular distribution. On either side of the neck, below the angle of the mandible, a solitary lymph node was enlarged and tender but no other lymph glands were palpable. She was given 300,000 units of penicillin in oil intramuscularly that day and on each of the next five days, a total of 1,800,000 units, without any beneficial effect on the course of the illness. Her temperature continued, fluctuating between 100.5° F. and 102° F. until January 4, 1949 and between 102° F. and 104.5° F. until January 7. The exudate, originally in a follicular pattern, now assumed a membranous appearance, involving not only the original sites, but the base of the tongue and the hypopharynx as well. The nasopharynx could not be seen but the clinical condition suggested involvement there, too. She developed a moderate cough with pain in the upper retro-sternal region. On January 5, the eighth day of the disease, the spleen was palpable. The submaxillary glands originally involved remained unchanged but a posterior cervical gland on either side became enlarged and tender. The patient was obviously quite toxic.

A blood count on the seventh day of illness revealed: hemoglobin, 16.7 gm. (104 per cent); red blood cells, 5,100,000; white blood cells, 9200 with a differential count of 33 per cent polymorphonuclear neutrophils, 65 per cent small lymphocytes and 2 per cent monocytes. The serum of blood taken the same day for heterophile antibody determination gave a positive agglutination in a dilution of 1:1792. Two throat cultures during the first six days were sterile for the diphtheria bacillus, positive for *Staphylococcus aureus* and gram negative diplococci.

Aureomycin was started orally at 1 p.m. on the tenth day of the disease on the morning of which the temperature reached 104.5° F. One hour before therapy was begun, however, the temperature dropped to 102° F. After 2.75 gm. were administered during the first 24 hours, the temperature dropped to 98.8° F. (figure 1). She received 2 gm. during the next 24 hours, her temperature varying between 98.8° F. and 100.5° F. After having had 3.75 gm. she developed some nausea and, on one occasion, vomited. The nausea, of slight degree, persisted for about 36 hours when she had two loose bowel movements. The dose for the third day, therefore, was reduced to 1.5 gm., a similar dose being given on the fourth day. The temperature assumed a normal level on the third day, there being no subsequent rise. A final dose of 1 gm. was given on the fifth day, making a total of 8.75 gm.

Twenty-four hours after treatment was begun, the patient no longer appeared toxic although she still had considerable dysphagia; the cough and retro-sternal distress disappeared; the spleen was no longer palpable; the enlargement and tenderness of the cervical glands were unequivocally less, reaching a normal state 96 hours after therapy was started. No other glands became palpable. There was no change in the pharyngeal exudate until 48 hours after the drug was begun, at which time several of the lesions began to shrink at their periphery and the dysphagia was minimal. Three days later, the throat was entirely clear.

\*Aureomycin was obtained through the courtesy of Lederle Laboratories Division, American Cyanamid Company.

A blood count done 24 hours after inception of treatment indicated a white cell count of 7800 with 35 per cent polymorphonuclear cells, 58 per cent small lymphocytes, 5 per cent large lymphocytes and 2 per cent eosinophiles. One done at the termination of treatment revealed 6200 white cells with 42 per cent polymorphonuclears, 51 per cent small lymphocytes, 1 per cent large lymphocytes, 4 per cent eosinophiles and 2 per cent monocytes. The heterophile antibody determination on the twenty-first day of the disease, 11 days after treatment was begun, showed a positive agglutination in a dilution of 1:896. On the next day, a blood count revealed the following: hemoglobin, 13.5 gm. (84 per cent); red blood cells, 4,200,000; white blood cells, 5,900 with 35 per cent polymorphonuclears, 51 per cent small lymphocytes, 3 per cent large

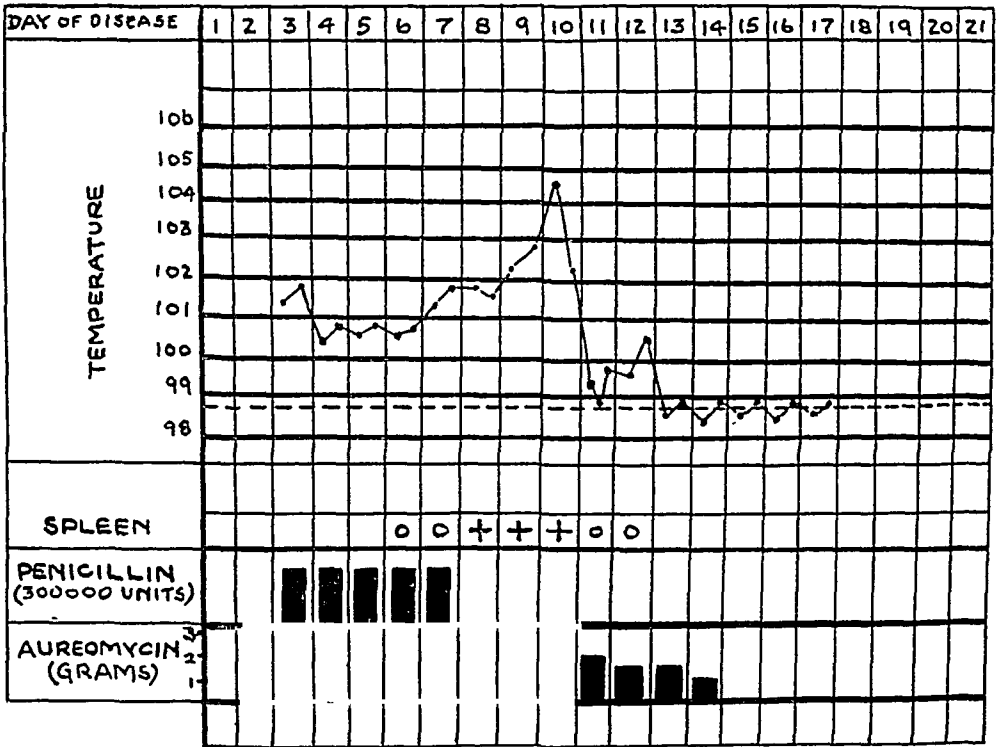


FIG. 1.

lymphocytes, 10 per cent eosinophiles and 1 per cent monocytes. The lymphocytes in all blood smears were abnormal to a large degree.

COMMENT

Infectious mononucleosis is, of course, a self-limited disease, lasting a few weeks to a few months, and it is extremely difficult to appraise any therapeutic agent in a disease of this type. McKinley and Downey,<sup>9</sup> analyzing a large group of cases, state that the temperature, after a daily increase during the first week, tends to subside, followed occasionally by one or two wave-like recrudescences before it becomes normal after a total duration varying up to 26 days. The average duration of illness of 45 cases was 14.4 days. However, they mention also that all the cases with prolonged course were those with some type of respiratory infection and with a marked degree of tonsillar and pharyngeal exudate. The

case reported here might well fit into that category and it may well be that the normal course of this patient's illness would have been prolonged. In this case, it is noteworthy that, coincident with the use of aureomycin, the following changes in the clinical course of the disease occurred within 24 hours:

1. A significant drop in temperature.
2. The spleen was no longer palpable.
3. The patient became markedly less toxic.
4. There was definite diminution in the swelling and tenderness of the cervical lymph nodes.

These observations warrant further clinical trial of aureomycin in infectious mononucleosis.

#### BIBLIOGRAPHY

1. DUGGAR, B. M.: Introductory paper, in Conference on Aureomycin—A New Antibiotic, New York Academy of Sciences, Section of Biology, July 21, 1948.
2. WONG, S. C., and COX, H. R.: Action of aureomycin against experimental rickettsial and viral infections, *Ann. N. Y. Acad. Sci.*, 1948, li, 290-303.
3. BRYER, M. S., SCHOENBACH, E. G., CHANDLER, C. A., BLISS, E. A., and LONG, P. H.: Aureomycin—experimental and clinical investigations, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 117-119.
4. FINLAND, M., COLLINS, H. S., and PAIN, T. F.: Aureomycin—a new antibiotic, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 946-949.
5. WRIGHT, L. T., SANDERS, M. S., LOGAN, M. A., PRIGOT, A., and HILL, L. M.: Aureomycin—a new antibiotic with virucidal properties, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 408-412.
6. SPINK, W. W., BRAUDE, A. I., CASTANEDA, M. R., and GOYTIA, R. S.: Aureomycin therapy in human brucellosis, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 1145-1148.
7. SCHOENBACH, E. B., BRYER, M. S., and LONG, P. H.: The pharmacology and clinical trial of aureomycin: a preliminary report, *Ann. N. Y. Acad. Sci.*, 1948, li, 267-279.
8. BRALEY, A. E., and SANDERS, M.: Aureomycin in ocular infections, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 426-427.
9. MCKINLEY, C. A., and DOWNEY, H.: *Oxford medicine* (Christian), 1944, v, 498.

---

### HYPERTROPHIC OSTEOARTHROPATHY; REPORT OF A CASE ASSOCIATED WITH A CHORDOMA OF THE BASE OF THE SKULL AND LYMPHANGITIC PULMONARY METASTASES \*

By NATHANIEL UHR, Lt. Col., Medical Corps, A.U.S., F.A.C.P., and  
JACOB CHURG, Captain Medical Corps, A.U.S.,  
*Topeka, Kansas*

MUCH knowledge regarding the clinical aspects of hypertrophic osteoarthropathy has been acquired in the past half century. Its etiology and mechanism, however, remain to be elucidated. In the majority of cases, osteoarthropathy, with its concomitant clubbing of the fingers and toes, is seen as a sequel of chronic suppurative or neoplastic disease of the thoracic organs, less commonly

\* Received for publication May 31, 1946.



of the abdominal viscera. Only in rare instances has the condition been known to precede the manifestation of the underlying disease. When this occurs, diagnosis is often impossible until late. The following is an illustrative case.

#### CASE REPORT

J. S., a 21 year old white prisoner of war, first became ill early in January 1944. The only significant illness in his past history was rickets during childhood which left him with slight bowing of the legs and moderate curvature of the spine. Up to the time of the present illness, he had felt entirely well and was able to perform hard manual labor. His weight in December 1943 was 168 pounds. Early in January 1944 he first began to complain of temporal and frontal headaches which were unrelieved by symptomatic treatment. Shortly afterward there developed lower abdominal pain associated with constipation and anorexia, and later, nausea and vomiting. Within a month there followed pain in the right side of the neck with torticollis and diminished hearing in the right ear. Upon admission to an Army Station Hospital on April 6, 1944, he had lost 25 pounds in weight and felt very weak. Physical examination at this time was recorded as negative save for slight fever, weakness and weight loss. Laboratory examinations of blood, urine, spinal fluid and basal metabolism were also negative except for slight anemia (hemoglobin 12 grams, red blood count 4 million), and elevated sedimentation rate (40 mm. per hour). Cholecystography, barium enema, and intravenous pyelography failed to disclose abnormalities.

The abdominal symptoms gradually subsided and the headaches became less severe. However, moderate fever up to 101° F., progressive weakness, and loss of weight continued. Aching pains in the limbs developed soon after admission, and clubbing of the fingers and toes became apparent. Roentgenograms revealed periosteal proliferation of the metacarpals and metatarsals, as well as of the bones of the forearms and legs. Roentgenographic examination of the spine was negative except for dorsolumbar scoliosis, and that of the skull revealed some irregularities in the region of the sella turcica which had the appearance of new bone production. A chest roentgenogram on April 26 was reported as normal. Early in May the patient began to complain of pain in the right lower chest aggravated by breathing. This symptom, at first intermittent, gradually became more severe and persistent with little relief until death. There was no cough nor expectoration. Fluoroscopy following the onset of chest pain revealed no cardiac nor pulmonary abnormality. However, a roentgenogram taken five weeks later disclosed infiltrative lesions of the right hilar and costophrenic areas (figure 2, c). The patient was transferred to a General Hospital for further investigation on June 15, 1944.

On physical examination at the time of admission, the patient appeared chronically ill and cachectic. The skin was dry and in many areas ichthyotic. The head could be rotated only with difficulty because of pain in the neck. There was exquisite tenderness of the right sternocleidomastoid muscle. Hearing in the right ear was markedly diminished. Moderate trismus was present. The pharynx could be seen sufficiently and was found normal. Except for tachycardia, the heart was normal. Blood pressure was 118 mm. Hg systolic and 75 mm. Hg diastolic. Examination of the lungs revealed impaired resonance with diminished breath sounds and showers of fine crepitant râles over the right lower lobe. Examination of the abdomen was negative. The fingers and toes were considerably clubbed with marked parrot-beak deformity of the nails. The forearms and legs were enlarged and thickened, giving the limbs a hypertrophic appearance in spite of the considerable atrophy of the musculature of the thighs and arms (figure 1, a and b). The patient experienced intense pain even on slight pressure over the long bones. Muscular weakness was marked in all the extremities. The cervical, axillary and other regional lymph nodes were not palpably enlarged. Rectal examination was negative. The prostate was normal to palpation.

but the testicles were much smaller than usual. Studies of ocular fundi disclosed slight papilledema with tortuosity of the veins, more marked on the left. These changes became more pronounced on subsequent examinations. Neurological examination one week after admission revealed exaggerated patellar and Achilles tendon reflexes, the sign of Babinski on the right and a questionable response on the left. Position sense was absent on the right and impaired on the left. Diplopia was noted when the object was at the extreme left; this became progressively more marked within the next two weeks. Bronchoscopy was attempted, but could not be performed because of trismus.

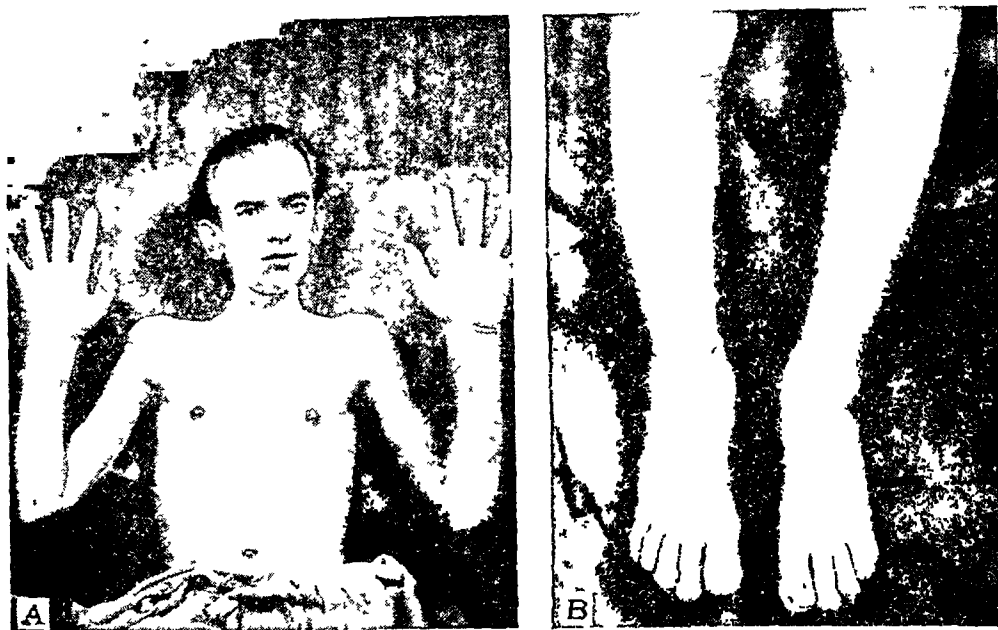


FIG. 1. *a* and *b*. Appearance of patient three weeks before death. Note thickening of forearms and legs.

The subsequent course in the hospital was dominated by increasing clinical and roentgenographic signs of pulmonary involvement. The patient developed cough with moderate expectoration. Rapidly increasing signs of infiltration of the right lung and pleural effusion were followed by similar involvement on the left. The periosteal changes became extremely marked (figure 2, *a* and *b*) and extended to the distal ends of the femora and humeri. Atrophy occurred about the joints. Roentgenograms of the skull revealed marked osteoporosis of the sella turcica with some erosion of the floor and the posterior clinoid processes (figure 2, *d*). The sedimentation rate was persistently elevated up to 52 mm. per hour. The blood calcium was 11.7 mg. per cent, phosphorus 4.2 mg. per cent, alkaline phosphatase 5.9 Bodansky units; white blood count and differential were within normal limits; red blood count was between 4.0 and 3.6 million, with hemoglobin between 12 and 10.8 grams per cent. During the last few days before death fever increased, with irregular elevations up to 103° F. Progressive embarrassment of respiration with cyanosis occurred and was followed by coma and death on July 14, 1944, approximately six months after the onset of symptoms.

*Autopsy.* The autopsy was performed eight hours after death. Only pertinent findings are recorded.

*Gross Examination. Skull:* The bones of the skull cut with usual resistance. The meninges were smooth, the subarachnoid fluid clear and colorless and not increased in amount. The vessels of the brain were markedly injected. The base of the

skull in the region of the sella turcica was elevated in an irregular fashion. The bone in this area was almost completely replaced by a firm grayish mass, uniform in appearance and consistency, except for occasional small grayish mucinous areas and embedded spicules of the original bone (figure 3, b). The mass extended to the pharyngeal vault, producing an ulceration about 2 cm. in diameter, and spreading under the mucosa along the posterior wall of the pharynx, into the nasal choanae and septum. On the cerebral side the mass elevated the entire sella turcica, destroying its floor and

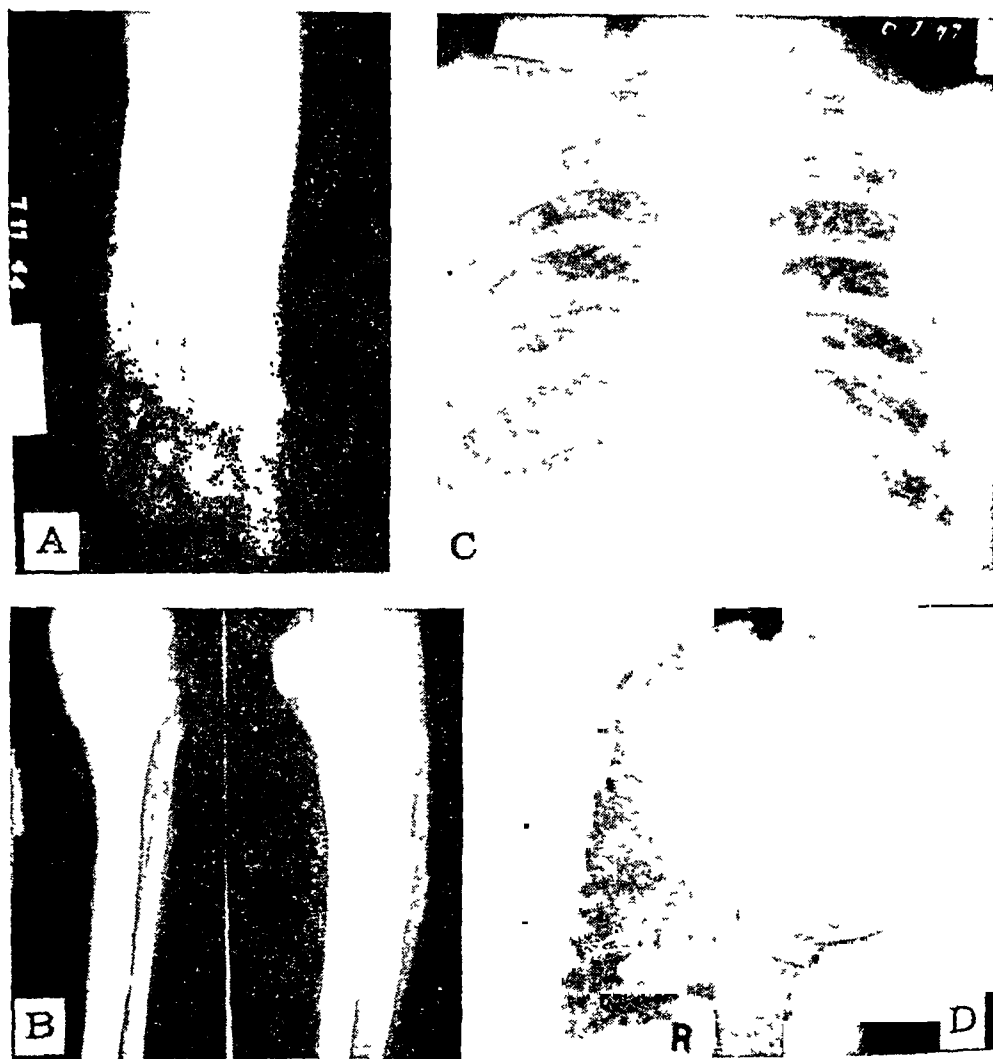


FIG. 2. *a* and *b*: Periosteal proliferation of the metatarsals and bones of the legs. *c*: Earliest pulmonary changes shown by roentgen-ray; involvement of the right hilus. *d*: Roentgenogram of the skull four weeks before death. Osteoporosis of the sella turcica

compressing and apparently invading the pituitary. It also raised the anterior part of the Clivus Blumenbachii and appeared to press upon the pons. However, at no point did it perforate the dura. Anteriorly, it spread into the sphenoid sinuses, and laterally into the cavernous sinuses, surrounding the carotid arteries. On the left the mass produced a dome-shaped elevation near the tip of the temporal pyramid and extended in the direction of foramen lacerum.

Examination of the brain after fixation revealed no significant abnormalities except for slight flattening of the pons.

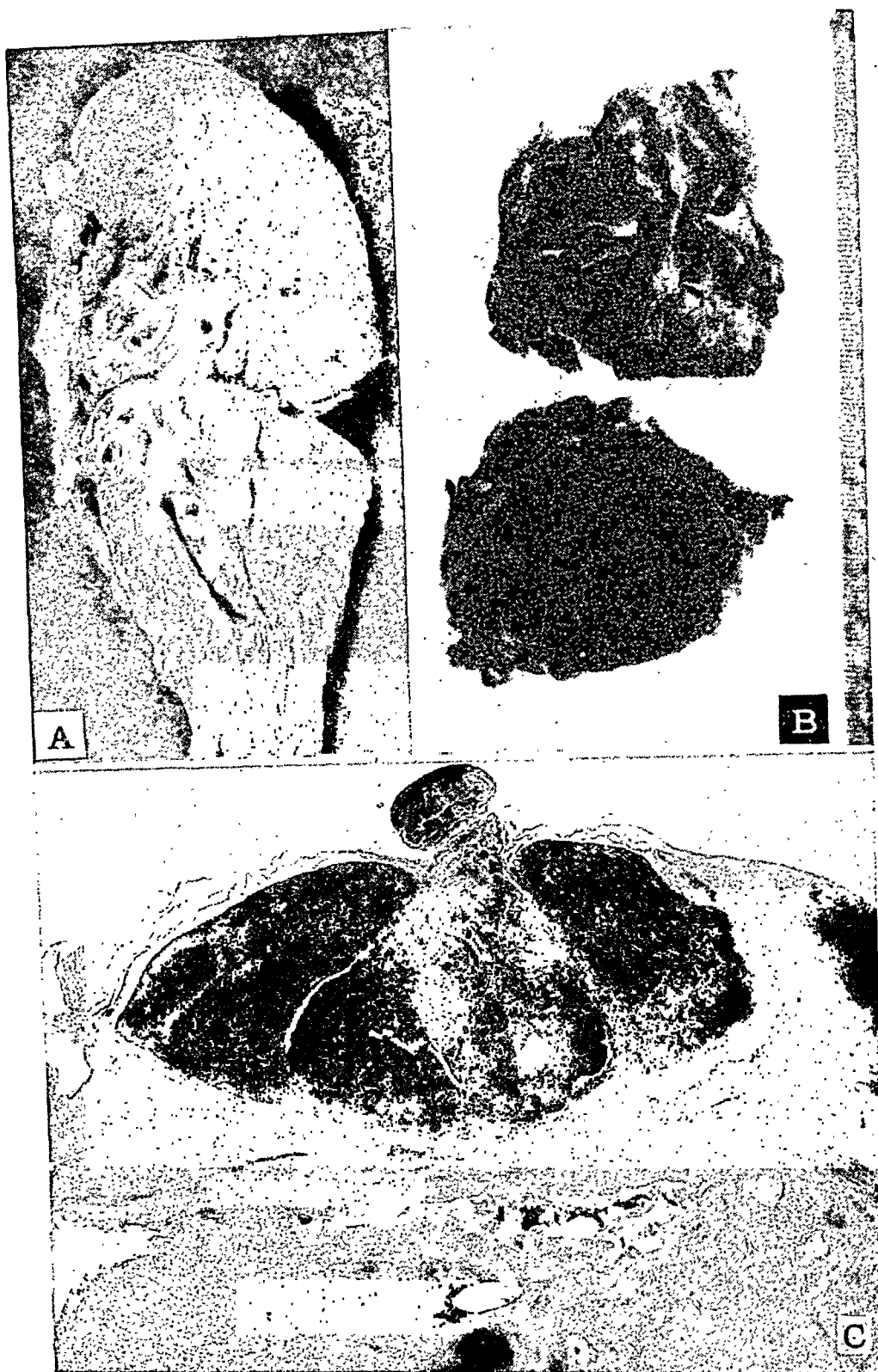


FIG. 3. *a*: Section of the right lung showing peribronchial and perivascular spread of the tumor. *b*: Tumor at the base of the skull and roof of the nasopharynx. *c*: Relation of the tumor to the pituitary gland. Note complete destruction of the sella turcica and the few remaining bony trabeculae within the tumor ( $\times 10$ ).

*Chest:* The right pleural space contained 1100 c.c. and the left, 300 c.c. of slightly bloody fluid. The lungs were bound to the walls of the chest by fibrous and fibrinous adhesions. The parietal and the visceral pleurae were covered by large confluent plaques composed of firm grayish-white tissue, varying in thickness from a few millimeters to a few centimeters. The lungs weighed 500 grams each; the left lung had three lobes. The parenchyma of both lungs was uneven in consistency, being firm in the hilar regions and softer although nodular towards the periphery. On section, the hilar structures were encased in dense firm grayish-white tissue which formed an almost continuous mass (figure 3, a). It followed the finer subdivisions of bronchi and vessels, forming a mantle of varying thickness. The right lower lobe was most extensively involved, but no part of the lungs was spared. In many places the tumor tissue had compressed and invaded the bronchial walls; however, there were no apparent breaks in the mucosa, and no complete obstruction of any of the lumina.

The lymph nodes of the posterior mediastinum, including the peribronchial, peritracheal and para-aortic, were large and firm. On section the normal markings were obliterated by dense grayish-white tissue. The abdominal para-aortic nodes above the level of the renal arteries showed similar changes. Other lymph nodes of the body were not abnormal.

The heart and the organs of the abdominal cavity showed no significant gross changes. The testes were small, weighing 10 grams each; the cut surface did not string well.

*Extremities:* The distal parts of all four extremities were thickened and enlarged. The hands and feet were covered with wrinkled skin. The terminal phalanges of fingers and toes were considerably thickened. There was cyanosis of the nail beds. The proximal half of the right fibula was removed. Its surface was markedly irregular and almost completely covered by thickened periosteum and newly formed cancellous bone (figure 5, a). On cross section, the original compact bone appeared unchanged. The marrow cavity was narrow and contained a small amount of reddish-yellow marrow.

*Microscopic Examination. Tumor in the base of the skull:* The bulk of the tumor below the sella turcica was composed of elongated or stellate cells forming a fairly loose syncytial meshwork (figure 4, a and b). The cells had quite abundant eosinophilic cytoplasm and large nuclei often containing distinct nucleoli. Many cells possessed large vacuoles in the cytoplasm giving them a "signet ring" appearance. The intercellular spaces were filled with pale, clear, faintly fibrillar substance suggestive of mucus. Here and there were occasional strands of connective tissue and small blood vessels, as well as small eroded spicules of bone. A few areas of necrosis were seen.

Towards the roof of the nasopharynx the tumor became more cellular (figure 4, c). The cells were smaller, more cuboidal in shape, with less cytoplasm and darker nuclei. They were often arranged in a single row around small irregular spaces and were surrounded by dense eosinophilic ground substance, reminiscent of connective tissue. There were fewer vacuolated cells and little intercellular mucus. In some places the cells markedly predominated over the ground substance; in other places they were widely scattered. In some areas clusters of loosely packed cells were found in the lymphatics. Blood vessels were not numerous. The tumor diffusely infiltrated the pharyngeal muscles and the mucosa, destroying the normal architecture; however, intact mucosa, glands and lymphoid tissue could be seen in many places. The ulceration was covered with necrotic tumor tissue and polymorphonuclear leukocytic exudate.

*Sella turcica and pituitary:* The tumor had completely destroyed the bony confines of the pituitary gland (figure 3, c). It also filled the cavernous sinuses, surrounding the carotid arteries. The pituitary gland was invaded in one area by tumor tissue similar in structure to that seen in the roof of the nasopharynx. The cells of

the gland were well preserved, the majority having distinctly eosinophilic cytoplasm. Along the periphery of the gland were several small areas of necrosis.

*Lungs:* Sections from various parts of the lungs showed a similar microscopic picture. The perivascular, peribronchial and subpleural lymphatics were markedly

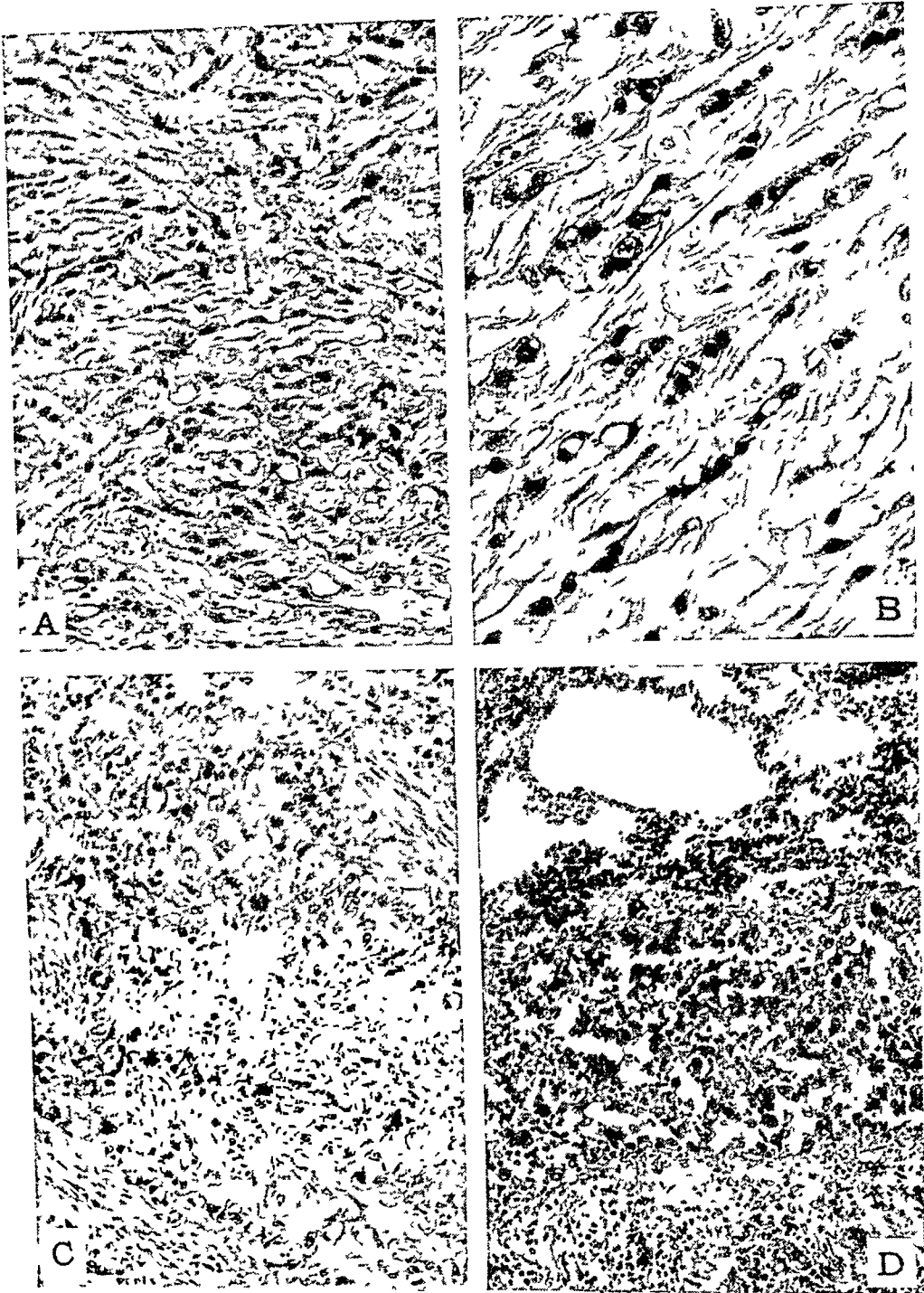


FIG. 4. *a* and *b*: Tumor at the base of the skull showing syncytial meshwork of elongated and stellate cells, "signet ring" cells and the faintly fibrillar, transparent intercellular substance (*A* -  $\times 180$ ; *B* -  $\times 350$ ). *c*: Tumor invading the roof of the nasopharynx. Variation in appearance of cells ( $\times 180$ ). *d*: Tumor cells in a pulmonary lymphatic ( $\times 160$ ).

distended with masses of tumor cells very similar to those found in the lymphatics of the nasopharynx (figure 4, d). The cells were polygonal but with poorly defined limits, giving the impression of a continuous though fairly loose syncytium. The cytoplasm was distinctly eosinophilic, and the nuclei, large and oval or polygonal. Only very few vacuolated cells were seen and there was no intercellular mucus. A considerable amount of necrosis was found in the larger nodules, with polymorphonu-



FIG. 5. *a*: Gross appearance of the right fibula. *b*: Cross section of fibula, showing thick periosteum and newly formed bone ( $\times 6$ ).

clear leukocytes intermixed with the tumor cells. In some areas the neoplasm appeared to break out of the lymphatics and infiltrate the adjoining parenchyma and the walls of the smaller blood vessels and bronchi. At one point, in the right main bronchus, the tumor had actually reached the lumen. The parenchyma especially in the right lower lobe was compressed and atelectatic; many alveoli contained edema fluid and polymorphonuclear leukocytes; others were filled with tumor cells. Occasional small blood vessels were occluded by fibrin thrombi.

*Pleura:* The pleura was markedly thickened by masses of tumor tissue, reproducing the structure of the tumor in the base of the skull. Small areas of elongated cells mixed with considerable mucinous intercellular substance, alternated in an irregular fashion with large areas of dense ground substance containing nests of cuboidal cells arranged about small empty spaces. There was a fair number of "signet ring" cells and also many elongated cells resembling fibroblasts. Areas of necrosis were fairly numerous.

*Para-aortic lymph node:* The lymphoid tissue was almost completely replaced by the tumor exhibiting the same pattern as in the pleural metastases. Some of the sinusoids and many of the lymphatics in the immediate vicinity were filled by syncytial masses of cells as seen in the pulmonary lymphatics.

*Testis:* Tubules were well developed but showed incomplete spermatogenesis.

*Fibula:* The original structure of the bone was well preserved, though widening of many of the Haversian canals suggested resorption. The marrow cavity was filled with fat. Superimposed upon the original cortex was a thick irregular meshwork of newly formed trabeculae, covered by thickened periosteum (figure 5, b). The intertrabecular spaces were filled with loose connective or fatty tissue containing occasional clumps of small round cells.

### COMMENT

The autopsy confirmed the clinical impression of extensive neoplastic involvement of the lungs, and massive hypertrophic osteoarthropathy. The changes at the base of the skull were caused by a malignant tumor identical in structure with that found in the chest. The involvement of the lungs was of "lymphangitic" variety with only secondary infiltration of the parenchyma, bronchial walls and blood vessels. There was no particular area which could have been designated as the primary focus. This fact argued against primary pulmonary neoplasm with metastases to the base of the skull. Reconsideration of the clinical course and detailed histological studies led us to believe that the converse, in fact, was true, that the tumor originated within the base of the skull and metastasized to the lungs and pleura.

The microscopic structure was characterized by the presence of fairly large elongated and polygonal cells with varying amounts of eosinophilic cytoplasm, often containing large vacuoles, and by abundance, in some areas, of clear intercellular mucinous substance. Though the typical "physaliferous" cells are missing, the polymorphous appearance with syncytial-like structure, vacuolization of the cytoplasm, accumulation of intercellular mucinous substance and tendency to arrangement around clear spaces, strongly suggest the diagnosis of chordoma. The topography of the tumor, the location of the most differentiated areas beneath the sella turcica, and the expansion of the involved bones testifies to the intraosseous origin of the growth. These features also help to exclude other tumors at the base of the skull, such as lympho-epithelioma and transitional cell carcinoma of the nasopharynx or sphenoid sinuses. The subsellar, intrasphenoid



craniopharyngioma might present similar gross features, but histologically it is usually a variant of squamous cell carcinoma.

Metastasizing chordomas of the base of the skull are not at all uncommon. Faust et al.<sup>1</sup> quote Mabrey's tabulation of 10 such instances among 27 autopsied cases of sphenoccipital chordoma, with involvement of lymph nodes, lungs, liver and other organs. However, even the malignant chordomas have a relatively slow course and may extend over a period of years. Cases such as presented here, with rapid course and massive "lymphangitic" metastases, must be very rare. Bruce and Mekie<sup>2</sup> postulated that tumors resembling the early stages of notochordal development with non-vacuolated polygonal cells are most malignant, while those resembling the later stages when cells become vacuolated and produce intercellular mucinous substance, are least malignant. In our case, vacuolated cells were in the minority, and intercellular substance was seen only in the central parts of the tumor, while the periphery, invading the pituitary and the nasopharynx, was characterized by non-vacuolated polygonal cells. Tumor thrombi in the lymphatics of the nasopharynx and the lungs contained cells almost exclusively of the latter type, whereas at the sites of secondary implantation, in the lymph nodes and the pleura, differentiation and production of mucus took place.

To reconstruct the pathogenesis of the disease, an expanding lesion in the skull first manifested itself in uncontrollable headaches. The headaches subsided spontaneously, perhaps at the time when the tumor broke through into the nasopharynx, thus relieving the tension. It is reasonable to assume that nausea, vomiting and other intestinal symptoms were also an expression of pressure on the brain stem and that their relief can be explained by the same mechanism. The subsequent neurological manifestations were caused not so much by increased intracranial pressure, as by direct pressure upon the brain stem. Infiltration of the nasopharynx accounts for trismus caused by reflex contraction of the internal pterygoid muscle, unilateral impairment of hearing, probably due to edema of the Eustachian tube, and torticollis, a manifestation of eleventh nerve involvement. The tumor invaded nasopharyngeal lymphatics, and, bypassing the cervical lymph nodes, metastasized to the chest. The pulmonary involvement produced no chest symptoms for a considerable length of time, during which it was confined to the lymphatics, yet it was accompanied by rapid and extensive hypertrophic osteoarthropathy. The changes in the long bones were typical of the latter condition. They consisted of marked deposition of newly formed bony trabeculae under the periosteum and thickening of the periosteum itself. The joints were not examined at autopsy, but roentgenograms demonstrated atrophic changes about the knees and ankles.

Various theories have been propounded to explain the mechanism of hypertrophic osteoarthropathy and clubbing of fingers. These have been discussed in a comprehensive and analytical review by Mendlowitz.<sup>3</sup> Many of the theories, such as trophic, nervous, infectious, etc., have only historical interest. Local circulatory disturbances have received considerable attention, with some authors ascribing the changes to capillary stasis, and others to increased blood flow.<sup>3</sup> Marie<sup>4</sup> and also Bamberger,<sup>5</sup> who were the first to describe hypertrophic osteoarthropathy, believed it to be caused by toxins emanating from the suppurative foci within the chest. However, the condition may follow neoplastic disease without infection. It is apparent that none of the theories thus far suggested can adequately explain all instances. Recently Fried,<sup>6</sup> in reporting four cases

of pulmonary neoplasm with hypertrophic osteoarthropathy, emphasized the similarity of certain aspects of this condition to acromegaly, and suggested dyspituitarism as a probable cause. This hypothesis was supported in his cases by acromegalic features, atrophy of testes and gynecomastia in the male, hirsutism and secondary male characteristics in the female, and also by hyperplasia of eosinophilic elements in the pituitary gland. In our case, except possibly for testicular atrophy, no evidence of endocrine dysfunction was observed, yet the pituitary gland showed distinct increase of eosinophilic cells in areas not involved by the tumor. More clinical observations and pathological data are required to establish the rôle of the endocrine apparatus and particularly the pituitary gland in hypertrophic osteoarthropathy. Until then, this theory must be considered an interesting but unproved possibility.

#### SUMMARY

1. A case of chordoma at the base of the skull is reported.
2. It is characterized by a high degree of malignancy, unusual for chordoma, by lymphangitic pulmonary metastases, and by early and massive hypertrophic osteoarthropathy.

We offer grateful acknowledgment for the assistance and suggestions given by Drs. S. B. Wolbach and Thomas D. Kinney and Dr. Sadao Otani.

#### BIBLIOGRAPHY

1. FAUST, D. B., GILMORE, H. R., JR., and MUDGETT, C. S.: Chordomata: a review of literature, with report of a sacrococcygeal case, *Ann. Int. Med.*, 1944, xxi, 678-698.
2. BRUCE, J., and MEKIE, R.: Chordoma, *Surg., Gynec. and Obst.*, 1937, lv, 40-47.
3. MENDLOWITZ, M.: Clubbing and hypertrophic osteoarthropathy, *Medicine*, 1942, xxi, 269-306.
4. MARIE, P.: De l'ostéo-arthropathie hypertrophiante pneumique, *Rev. de méd.*, 1890, x, 1-36.
5. BAMBERGER, E. VON: Ueber Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten, *Ztschr. f. klin. Med.*, 1890, xviii, 193-217.
6. FRIED, B. M.: Chronic pulmonary osteoarthropathy. Dyspituitarism as probable cause, *Arch. Int. Med.*, 1943, lxxii, 565-580.

### A CASE OF A PUTRID EMPYEMA WITH A BRONCHO- PLEURAL FISTULA SUCCESSFULLY TREATED WITH PENICILLIN \*

By ARTHUR L. FORSGREN, M.D., *Minneapolis, Minnesota*

RAPID advances have been made in the treatment of empyema thoracis with the advent of penicillin, especially with its use intrapleurally. In all probability,

\* Received for publication March 24, 1947.

From Veterans Administration Hospital, Minneapolis, Minnesota, and the Department of Medicine, University of Minnesota.

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

the full therapeutic potentialities of penicillin have not been fully explored. The classical indications for surgical intervention in the treatment of empyema have been modified extensively by penicillin. Finland et al.<sup>1</sup> expressed the opinion that more than one-half of all cases of empyema can be cured by repeated aspirations and local instillations of penicillin into the pleural cavity.

There is general agreement that certain indications for early surgical treatment persist. Included among these indications are: the presence of a putrid

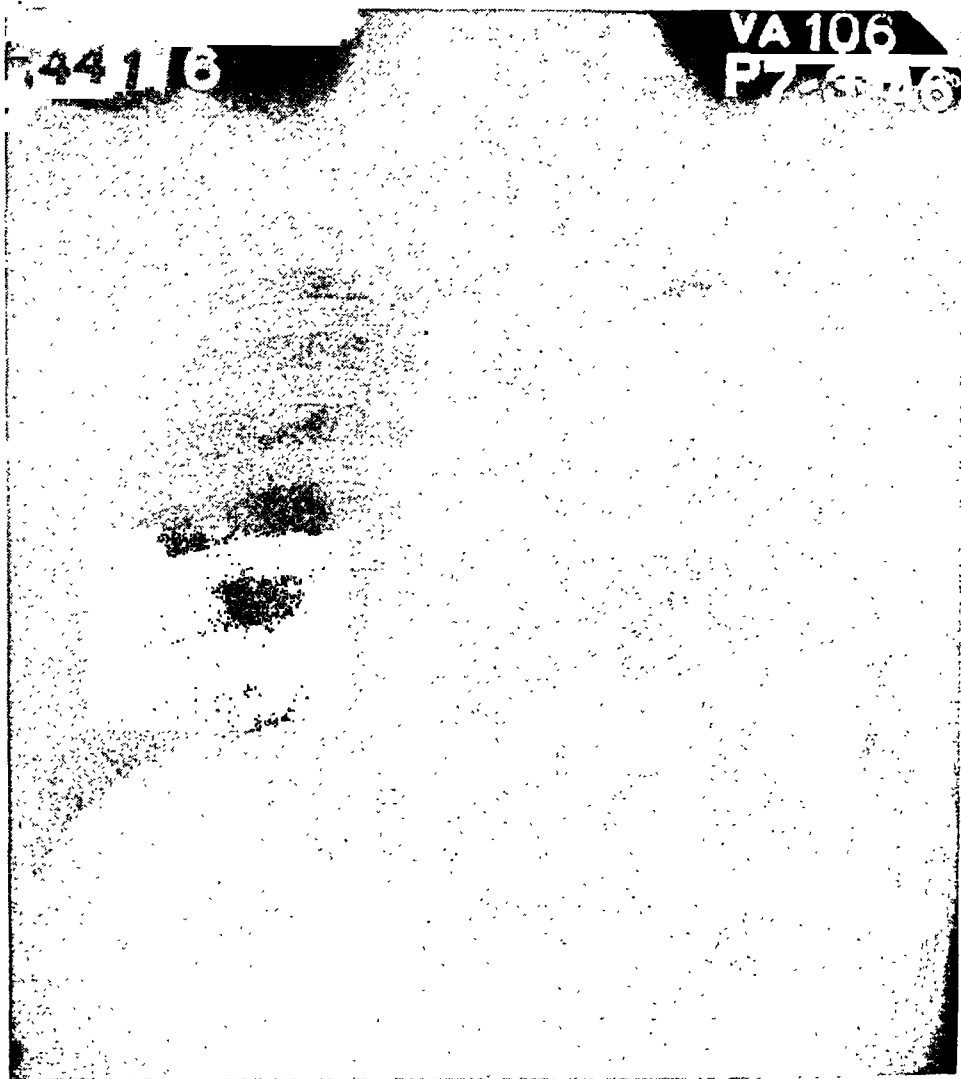


FIG. 1. Photograph of roentgen-ray before therapy.

empyema, and broncho-pleural fistula. In their review of the literature, Finland et al. mention five cases of putrid empyema that were treated with intrapleural penicillin instillations without surgical drainage. Of these five cases, two were cured. In these two cases the putrid empyema was further complicated by the presence of broncho-pleural fistulae.

The following case is of interest in that, in spite of putrid empyema contents

and a broncho-pleural fistula, the patient made a surprisingly prompt and uneventful recovery under intensive penicillin therapy. The patient received intramuscular penicillin, penicillin aerosol, and intrapleural instillations of penicillin.

The concomitant existence of a broncho-pleural fistula, in the cases of putrid empyemas successfully treated medically, demonstrates that such a fistula can

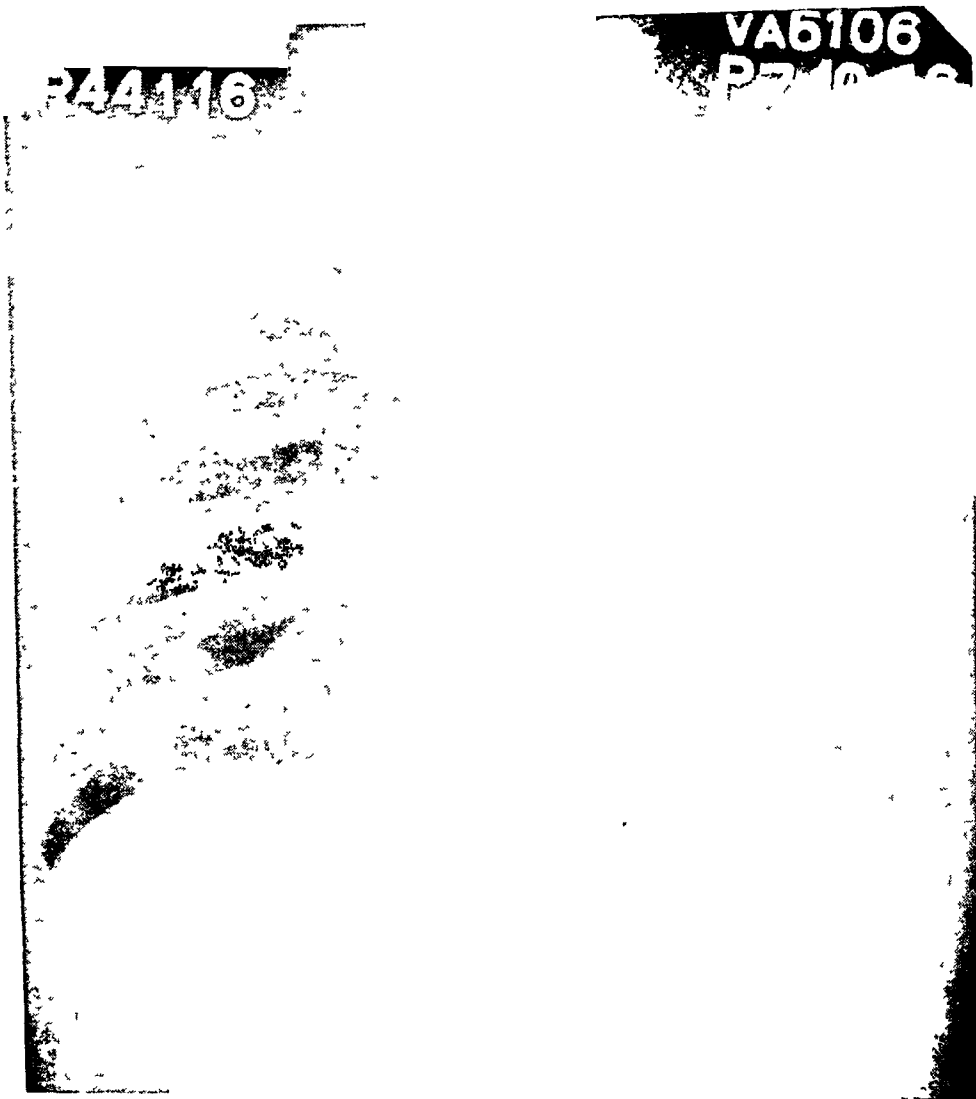


FIG. 2. During therapy.

heal without open drainage if the infection can be controlled. It also suggests that the fistula might have served a useful purpose in emptying the empyema cavity.

#### CASE REPORT

A 52 year old farmer first became ill during the last week of May, 1946. At this time he noted a sudden onset of chills and fever subsequent to the extraction of three abscessed teeth. The following day he had severe, anterior left chest pain on

respiration. He was told by his physician that he had pleurisy and was given penicillin intramuscularly every four hours for six days. The chest pain subsided but his fever persisted. He had only a slight cough at this time.

On June 4 he was admitted to a local hospital with complaints of fever, weakness, anorexia, and weight loss. A diagnosis of probable pulmonary abscess was made at that time. Treatment consisted of intramuscular penicillin for two weeks and a course of a sulfonamide for one week. About June 20 the patient suddenly developed a severe cough productive of large amounts of greenish sputum.

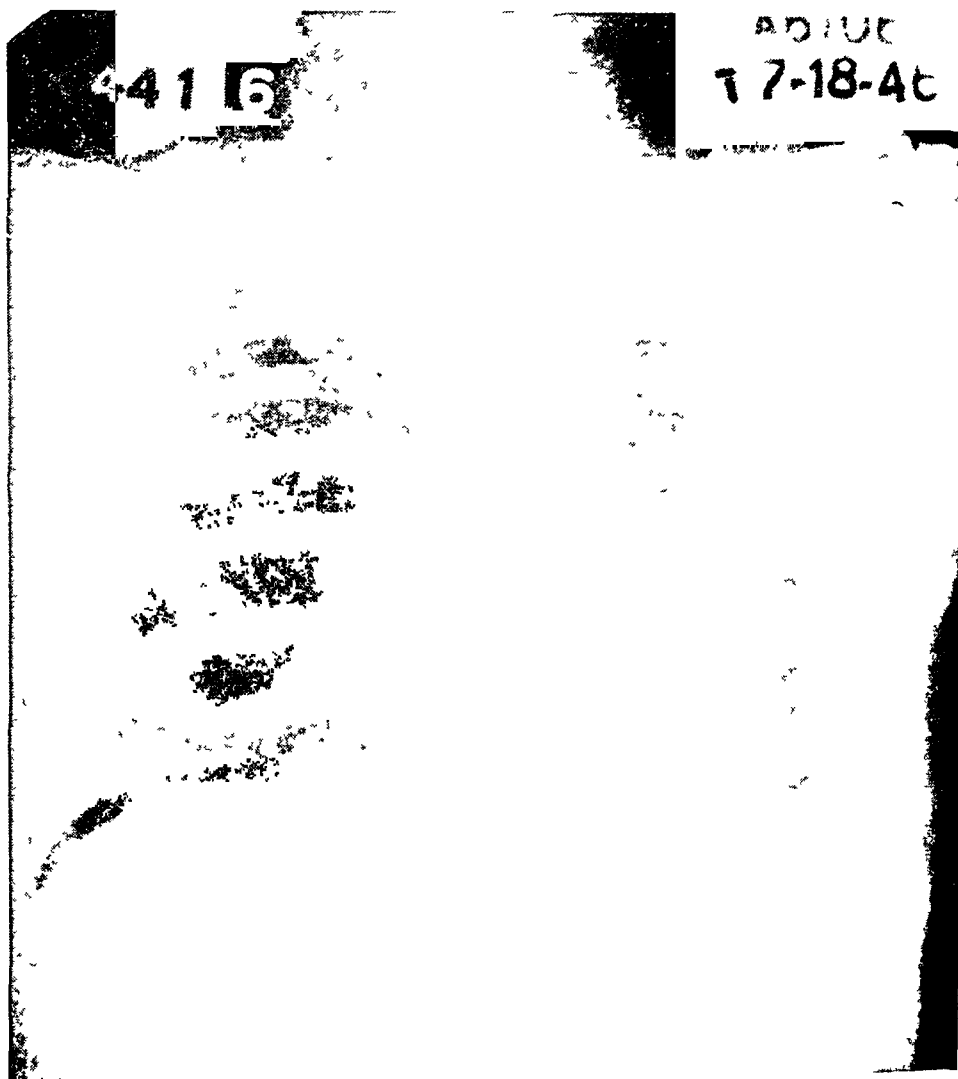


FIG. 3. During therapy.

On July 2 he was transferred to the Veterans Administration Hospital in Minneapolis. At this time his complaints included fever, productive cough, malaise, anorexia, and weakness. Physical examination revealed a well-developed 52 year old white male who showed evidence of recent weight loss. Temperature was 102.4°, pulse 104/min., respiratory rate 24/min. The patient weighed 155 pounds, in contrast to his usual weight of 185 pounds. Blood pressure was 140/82 mm. Hg. The teeth

were carious and moderately advanced pyorrhea was present. There was mucopurulent material in the pharynx. No cardiac abnormalities were noted; no organs or masses were palpable in the abdomen.

Examination of the chest revealed slight atrophy of the muscles over the left chest. The right lung was normal to auscultation and percussion. There was resonance over the left anterior lung, in the left axilla, and over the extreme upper portion of the left posterior lung. The lower three-fourths of the left posterior lung revealed dullness to flatness on percussion; tactile fremitus was decreased over this

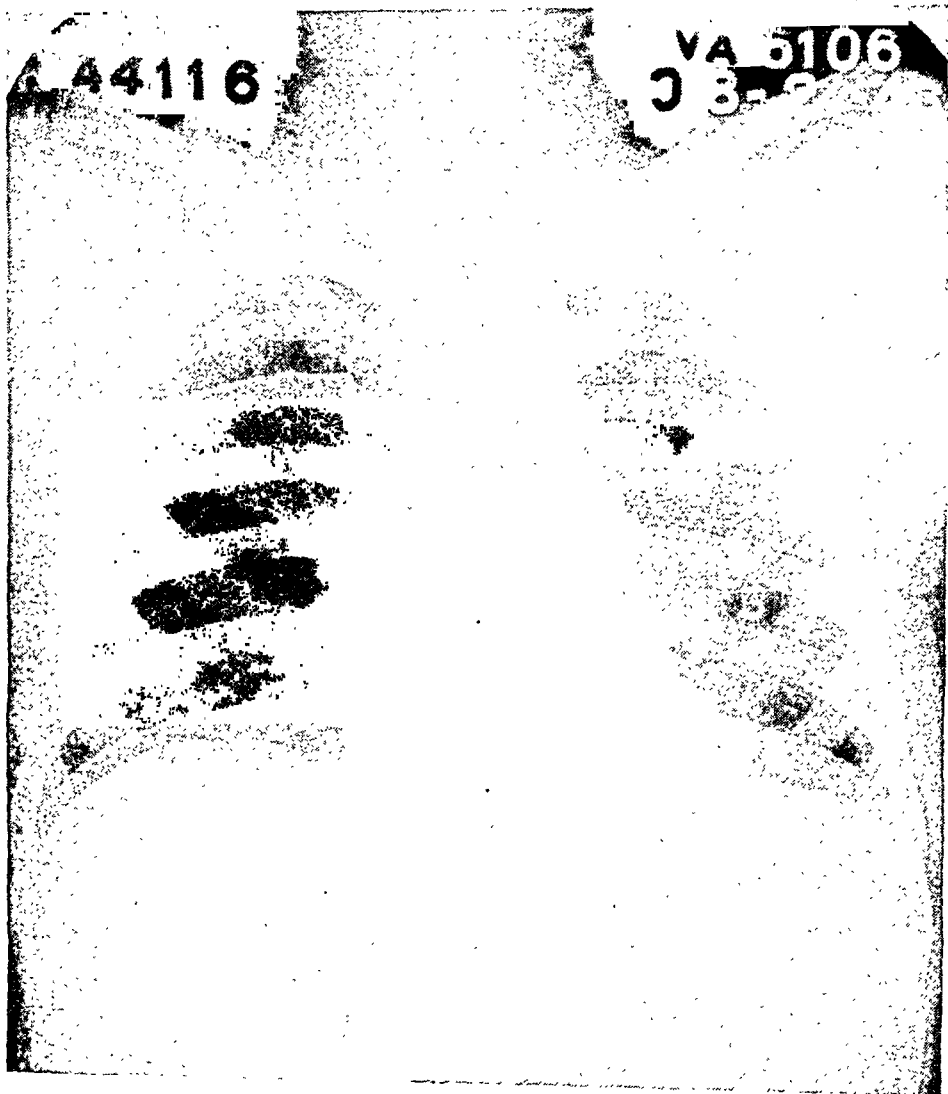


FIG. 4. After therapy.

area and the breath sounds were diminished though bronchial in quality. The sputum was green, purulent, and odorless.

Laboratory studies on admission showed the hemoglobin to be 11.8 gm., with 3,680,000 red blood cells. White count was 14,400, with 82 per cent neutrophils, 15 per cent lymphocytes, and 3 per cent monocytes. Urinalysis showed a specific gravity of 1.015, with albumin and sugar negative. Postero-anterior chest roentgen-ray showed a density involving almost the entire left chest with an airfluid level in

Day of observation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38
Temperature																																						
WBC	<div>14,400</div> <div>12,300 11,600</div> <div>7,200</div> <div>7,500</div> <div>6,750</div>																																					
Thoracenteses (c.c.)	<div>250 200 150 75 75 Dry tap</div>																																					
Culture	<div>Non-hem. strep. + + + 0 0 0</div> <div>A. aerogenes + 0 0 0 0</div>																																					
Intrapleural penicillin (u.)	<div>100,000</div>																																					
Intramuscular penicillin (u.)	<div>40,000 q.3 h.</div> <div>50,000 q.3 h.</div>																																					
Nebulized penicillin (u./c.c.)	<div>20,000 10 min. q. 2 h.</div> <div>20,000 15 min. q.i.d.</div>																																					
Weight (lb.)	<div>156 157 157 158 158 161 162 163 165 170</div>																																					
Lungs																																						

It was felt at this time that the patient presented the problem of a putrid empyema with a probable broncho-pleural fistula. It was decided, in conjunction with the thoracic surgeons, to defer any surgical intervention for a period of one week to 10 days, during which time an intensive therapeutic program with penicillin was to be carried out. The treatment instituted consisted of the following: 100,000 units of penicillin in 50 c.c. normal saline were instilled into the empyema cavity following aspiration of the empyema fluid every 48 hours. Forty thousand units were given intramuscularly every three hours, and penicillin was nebulized for 10 minutes each hour in concentration of 20,000 units per c.c. Postural drainage was carried out several times daily with raising of 100 to 250 c.c. of sputum daily. During the third instillation of penicillin into the pleural cavity the patient stated that he could taste the penicillin. A small amount of Evans blue dye was added and the patient promptly coughed up bright blue sputum. This definitely established the existence of a broncho-pleural fistula.

*Aerobacter aerogenes* was no longer cultured from the empyema fluid after the first aspiration. The non-hemolytic streptococcus persisted until after the third penicillin instillation. This organism was shown to be sensitive to 0.2 unit penicillin per c.c. in vitro.

After four penicillin instillations there was marked clinical improvement. Surgical intervention was not considered necessary. Chest roentgenograms showed marked diminution in the size of the cavity and in the amount of fluid. No fluid was obtained on thoracentesis. Intramuscular and nebulized penicillin was continued for two weeks, during which time the patient became asymptomatic and afebrile, the cough disappeared, and the white blood count fell to 7,500. The vital capacity increased to 2.9 liters. On August 1 all penicillin was discontinued. Chest roentgen-ray showed evidence of thickened pleura, as did physical examination, but no encapsulated fluid could be visualized. At this time the patient had gained 15 pounds since admission. The patient was discharged from the hospital on August 9, eight days after discontinuation of penicillin, no symptoms, febrile reaction, or positive physical findings having recurred.

The total period of hospitalization following diagnostic thoracentesis was four and one-half weeks.

Fifteen weeks after discharge from the hospital the patient was entirely asymptomatic and engaged in his normal farming activities:

### CONCLUSION

A case is presented demonstrating the cure of a putrid empyema with a broncho-pleural fistula obtained with penicillin therapy.

### BIBLIOGRAPHY

1. BROWN, BRUCE, ORY, EDWIN M., MEADS, MANSON, and FINLAND, MAXWELL: Penicillin treatment of empyema: report of 24 cases and review of the literature, *Ann. Int. Med.*, 1946, xxiv, 343-370.



## EDITORIAL

### *THE ELECTROENCEPHALOGRAM*

THE recent appearance of Electroencephalography and Clinical Neurophysiology ("The EEG Journal") under the auspices of the International Federation of EEG Societies serves to emphasize the growth and the increasing importance of this highly specialized field of medicine. Almost everyone has heard of the "brain waves" and is aware that they are used in diagnosis. Many, however, even among physicians, do not know precisely in what disorders the EEG is really useful in diagnosis and particularly are not aware of its present limitations. Some knowledge of the nature of the observations on which conclusions are based, as well as of sources of error both in technic and in interpretation, may help to clarify the subject.

That changes in electrical potential accompany cortical activity has been known for many years. Thus Caton (1875), working with the exposed brain of experimental animals, noted "feeble currents of varying direction" when electrodes were placed on two points of the external surface. To detect and usefully record these differences on the scalp, where their amplitude is greatly reduced, was impossible until technical methods of amplification had been perfected. Berger (1929) was the first to accomplish this, but at first his observations were distrusted, and they were not confirmed until 1934 by Adrian and Matthews.

In a tracing from a normal adult, amid the apparent jumble of waves one may make out in the relaxed waking state sequences of similar rhythmic waves of two characteristic types.\* The alpha waves appear as smooth waves with a rounded tip, of moderate amplitude (average about 35 microvolts) and at a frequency of about 8 to 12 per second, dominant occipitally. Normally these are usually synchronous and about equal in amplitude in symmetrical areas in the two hemispheres. Less often there are series of "low voltage fast" activity, beta waves, with an amplitude of about 10 microvolts or less and a frequency of 18 to 30 per second, dominant centrally.

The occurrence of such waves shows clearly that the cortical cells do not "discharge" in a haphazard fashion but that large numbers of them discharge in unison in a regular rhythmic manner. A disturbance of such rhythmic sequences is often referred to as cerebral dysrhythmia. The exact mechanism of the production of these electrical changes is not known. Normal activity of the cortical cells is essential, but there is good reason to believe that it is at least regulated by deeper structures, possibly the thalamus. They may be affected by physiological cerebral activity. Thus alpha waves tend to be depressed or abolished by mental concentration or visual stimulation, and this factor must be considered in the interpretation of the records.

The alterations in the tracings which are observed in pathological conditions may be of several different types. There may be a general dis-

organization of the pattern with loss of the regular sequences of rhythmic waves. The amplitude may be increased or diminished. There may be bilateral asymmetry, either in frequency or amplitude, of the waves. There may be "slow" waves (less than 8 per second), either isolated "random" waves, focal or diffusely scattered over the head; or such waves may come in regular sequences which are of great significance, especially if their amplitude is high. "Spikes" may occur, similarly distributed, brief, sharp-tipped waves, often of high amplitude.

Finally there is the well known "wave-and-spike" or "spike-and-dome" pattern, usually occurring in regular rhythmic series and generalized. This is always found during a clinical petit mal seizure, is often present in such cases in intervals between clinical seizures, and occurs occasionally between seizures in patients with convulsive attacks in whom no clinical petit mal seizures have been recognized. Although virtually pathognomonic of idiopathic epilepsy, this pattern has been reported as a sequel of encephalitis in children.

The first major application of the EEG to clinical diagnosis and perhaps the most important was in epilepsy, following the observations of Lennox and Gibbs. Immediately preceding a grand mal seizure highly characteristic changes occur, consisting often of numerous spikes associated with and eventually replaced by a generalized sequence of rhythmic slow waves of high amplitude. In the interval between seizures in some cases there are occasional short sequences ("bursts") of spikes, rhythmic slow waves, or both. Quite frequently there are only random scattered slow waves which are abnormal but not in themselves diagnostic, and in about 15 per cent of the cases no clear cut abnormality can be found.

The wave-and-spike pattern of the petit mal seizures has been noted. In "psychomotor epilepsy," episodes of abnormal behavior regarded by some as an "epileptic equivalent," Gibbs has described slow, notched or flat-topped waves, but others have questioned their significance as a manifestation of epilepsy.

Finally there is a group of clinically normal individuals, according to some constituting up to 15 per cent of the population, whose records show non-specific abnormalities, usually of minor degree.

Focal destructive lesions involving the cortex, including tumors, abscesses, local traumatic lesions, subdural hematoma and scars resulting from such lesions, cause definite abnormalities in many cases. The commonest manifestation of superficial cortical lesions is the occurrence of random slow waves, generally not equal or rhythmic, which are usually localized. More rarely there may be spikes alone or a mixture of spikes and slow waves, but only if the electrode is close to the tumor. There may be a similar disturbance in the symmetrical area on the other side but usually of lower amplitude. The abnormal waves do not arise from the tumor, which electrically is relatively "dead" tissue, but from the damaged cortex at the margin of the tumor. In the case of deep tumors the disturbance may be generalized.

Walker has used this procedure to localize lesions (especially epileptogenic foci) precisely by applying electrodes to the exposed cortex and determining the exact area from which spikes arise. This can rarely be accomplished over the scalp, and other devices must be employed. One such is the demonstration of a "phase-reversal" of the electrical potential in the region of a tumor. If simultaneous tracings are taken with a series of electrodes arranged in a semicircle about the head and passing over or near the tumor, a distinctive abnormal wave may have a negative potential as one approaches the tumor and a positive potential as one passes away from it.

There are no criteria by which the various types of focal lesions can be distinguished with certainty by the EEG. The latter merely indicates a focus of abnormal electrical activity associated with injured cortical tissue. A more precise diagnosis can often be reached, however, in conjunction with the clinical history and the results of a neurological examination and other special procedures. Negative findings do not exclude a focal lesion.

The EEG is a valuable means of detecting cerebral damage following head injuries. In the acute stage, if the injury was severe and brain tissue damaged, abnormalities can almost always be demonstrated. These may closely resemble those seen in idiopathic epilepsy, but they have no prognostic significance unless they persist. In that event convulsive seizures eventually are prone to develop. In general these abnormalities tend to disappear gradually during the first six months, and in most cases largely or completely by the end of a year. Lesser changes may persist indefinitely, however, such as disorganization of the wave patterns, scattered slow waves, and depression of alpha waves, usually on the affected side. Similar changes are seen occasionally in clinically normal persons, and it has been suggested that they may be sequelae of unrecognized head injuries in childhood. In the cases with minor contusions or mild degrees of concussion there are usually no abnormalities.

The EEG has also been used in a study of degenerative processes such as cortical atrophy, porencephaly, and infarcts. In cases of longstanding hemiplegia there is usually but little abnormality in ordinary records. In sleep records, however, depression of the fast component has been reported, and also a reduction in the response to auditory stimulation on the affected side.

In acute encephalitis there are always abnormalities which gradually disappear unless cortical injury is severe.

Metabolic disorders may also cause alterations in the EEG. Hypoglycemia in a degree insufficient to cause clinical symptoms may cause changes which could be mistaken for epilepsy or organic cerebral disease. These can be eliminated by administration of glucose.

In the neuroses and ordinary functional psychoses the EEG has been of no positive value in diagnosis. No distinctive changes have been recognized, and the proportion of cases showing nonspecific abnormalities is no greater than in the general population.

As already noted, normal records are obtained in a significant percentage of patients with epilepsy or organic brain disease. Various procedures have been tried to elicit abnormalities in such cases, of which hyperventilation is the most useful and is now practically a routine procedure. Even in normal individuals, however, and particularly in children it tends to cause disorganization of the pattern and slowing of the activity, and care must be used in the interpretation. Injections of metrazol have been used, but the technic has not been adequately standardized.

Sleep or drowsiness causes marked changes in the EEG, depending upon the depth of sleep. The most important are a general slowing of the rate and the appearance of irregularly distributed slow waves of high amplitude which may be interpreted by the unwary as indications of disease. There is also a fast component, sequences of waves at 12 to 14 per second that often appear in the form of "spindles."

Records taken during sleep often yield information not obtained in waking records, particularly if they include shifts between the waking and sleeping state. Sleep may be natural or induced by hypnotics, of which seconal seems at present to be the most satisfactory. The characteristic changes in epilepsy may often be induced in this way; these are not masked by sleep, but they can be more easily recognized. Sleep markedly lessens the artefacts in the records due to gross muscular movement or tension, and it may be the only way of obtaining records in hyperkinetic or unruly children.

To be of value it is essential that the test be carried out with meticulous care by a thoroughly trained technician. The requirements in this respect are far more exacting than for any of the other diagnostic procedures in common use. Artefacts arising from technical errors or mechanical defects in the apparatus may simulate almost any of the pathological alterations that have been described. Particularly disturbing are spikes and waves of increased amplitude, either scattered or in sequence. Among the commoner sources of trouble are poorly applied or loosened electrodes, improperly placed electrodes, spread of electrode paste, sweating, swaying of the electrode wires, restless movements of the patient, blinking of the eyes, unrecognized drowsiness, faulty or "noisy" vacuum tubes and static electrical disturbances arising from sparking motors, diathermy or roentgen-ray machines. Tension or twitching of the cranial muscles, especially the temporals, causes "muscle spikes" which may obliterate other features of the tracing or, if sparse, may be mistaken for spikes of cortical origin.

The individual who interprets the record must be familiar with these artefacts and differentiate them from significant alterations. This is not always easy. He must be familiar with the standards of normal, which vary with age. In normal infants the records are poorly organized and show predominantly irregular slow activity. The shift to the adult pattern is gradual and is not usually attained until the fourteenth to eighteenth year. The record of any normal child is, therefore, likely to show aberrations from the adult pattern which would be pathological in an older age group.

He must be familiar with the degree of abnormality which may be anticipated in certain clinically healthy individuals. There is no general agreement as to this, and it is impossible to distinguish sharply between normal and abnormal records. If the criteria of normal are made so strict as to exclude most of the "false negatives," a disturbing number of misleading "abnormal" records will be obtained. In general the abnormalities in these "border-line" records should be regarded as of no diagnostic significance in themselves. In a patient with known or suspected disease, they may have some confirmatory value if they are characteristic, and they indicate the need for repeated tests and possibly special procedures to secure more definite information.

Finally, the individual who interprets the record must have all the information available regarding the patient if the test is to be really useful and dependable. With the possible exception of a minority of the cases of idiopathic epilepsy, it is rarely if ever possible to make a conclusive diagnosis on the basis of an EEG alone. It is often of great value in differential diagnosis, however, in cases of organic disease in which the nature of the lesion is in doubt; e.g., if there is a question as to epilepsy, tumor or a traumatic lesion.

If the referring physician lacks the technical knowledge and experience required to interpret the record himself, this clinical information must be supplied to the one making the test. For example, patients who have received treatment with electroshock show sequences of slow waves of high voltage which gradually disappear after treatment is stopped but may persist in some degree for six months to a year. If this is not known, a gross misinterpretation is likely to result. Furthermore, if this information is available before the test is carried out, it often helps greatly in selecting those procedures most likely to reveal abnormalities in a given case. To withhold information in order to secure an unbiased opinion defeats its own purpose.

An EEG, therefore, furnishes information of great diagnostic value in many suitably selected cases, if it is properly made and interpreted with discrimination in conjunction with all the other information available.

P. W. C.

## REVIEWS

*Clinical Allergy.* By LOUIS TUFT, M.D., Assistant Professor of Medicine, Temple University School of Medicine; Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital, Philadelphia, Pennsylvania. Second edition. 690 pages; 16 × 24 cm. Lea and Febiger, Philadelphia 6, Pennsylvania. 1949. Price, \$12.00.

In the opinion of this reviewer, Dr. Tuft's book is the best text on allergy available. The present volume is planned along lines similar to those followed in his original, or previous edition. However, it has been thoroughly rewritten and is modern in every sense. The volume is attractive in appearance, is a reasonable size, the type is clear, and the subject matter well arranged.

The author has retained his basic method of presentation in that the major divisions of the text are unchanged. First, general considerations of allergy are presented with a satisfactory discussion of the basic facts of anaphylaxis and allergy. This serves as an adequate orientation for the uninitiated and, in addition, will bring the practicing allergist abreast of current thinking about important phases of these subjects. The author then discusses etiological agents in groups, pointing out the important group characteristics of different types of allergens and calling attention to the clinical significance of these facts.

His discussion of the clinical manifestations of allergy, that is, the conditions one must treat practically, is sound, complete, and sufficiently free from confusing speculation to make it of great value in the clinical application of the vast amount of data his book contains.

In his discussion of the treatment of asthma, those of us who have used Butane-frine extensively will be disappointed to find no mention of this very valuable drug; particularly, when one considers the space given to other agents of doubtful value, some of which he condemns. This omission is difficult to understand.

This volume is a textbook in the best sense of the word. It is sufficiently dogmatic to permit the reader to chart a course clinically. Pertinent facts are given, doubtful data have been omitted. The author, also, avoids the temptation to coin new phrases and to add new classifications to the multiplicity of these now extant that dog the beginner in his attempt to see different phases of allergy clearly and with understanding.

Brief summaries of the different sections are again introduced with profit as are the comparative tabulations of differential diagnostic criteria in those conditions showing confusing similarities.

The section in which data are given on the place of occurrence of allergens and the technical procedures peculiar to allergy, is most valuable.

The newly included material on molds and antihistaminics is excellent and is presented with brevity and clarity as is usual with this author. However, the omission of the excellent bibliography included in the original edition represents a distinct loss, and it is unfortunate that the publishers deemed this necessary.

This book will be of great service to all physicians desiring to increase their knowledge of allergy. This should include all members of the profession.

H. M. B.

*Clinical Auscultation of the Heart.* By SAMUEL A. LEVINE, M.D., Clinical Professor of Medicine, Harvard Medical School; Physician, Peter Bent Brigham Hospital; and W. PROCTOR HARVEY, M.D., Research Fellow in Medicine, Harvard Medical School, Assistant in Medicine, Peter Bent Brigham Hospital. 327 pages; 15 × 23.5 cm. W. B. Saunders Co., Philadelphia. 1949. Price, \$6.50.

This text deals with the information that can be obtained by the use of the stethoscope, "such an inexpensive and expedient tool." It contains many interesting and valuable details concerning both normal and abnormal heart sounds. For example, the authors point out that the first heart sound may be accentuated when the P-R interval is shorter than normal, because of the position of the A-V valves so soon after auricular contraction. They describe the "inching procedure" to differentiate systolic from diastolic gallop sounds. They state that in general the sounds of an auricular premature beat resemble the normal beats of that particular patient and that the sounds of a ventricular extrasystole are different. There is some confusion when the authors attempt to differentiate between the normal third heart sound, the opening snap of mitral stenosis, and the protodiastolic gallop sound. The important problem of the diagnosis of rheumatic mitral insufficiency in the absence of mitral stenosis is solved by basing the diagnosis not upon the intensity of the murmur alone, but also upon the history, the presence of some cardiac enlargement and an abnormal fluoroscopic appearance of the left auricle.

In general the descriptive material can be read with interest and profit. The caption for figure 240 is incorrect, and should read "subaortic stenosis" rather than "subacute stenosis." The book is abundantly illustrated with 286 figures, chiefly stethograms which do not equal the written text in quality. There are 35 pages of index for the 291 pages of text and figures. It is regrettable that this book, which brings together much information concerning auscultation of the heart, contains no bibliography to which the reader may refer for the basic studies in this important field.

S. S.

*Correlative Neuroanatomy.* By J. J. McDONALD, J. G. CHUSID, and J. LANGE. 156 pages; 17.5 × 25 cm. University Medical Publishers, P. O. Box 761, Palo Alto, Calif. Fourth edition, revised. 1948. Price, \$3.00.

It is not a simple matter to determine what actual value a book such as "Correlative Neuroanatomy" has. It is in the nature of such a compendium that the dynamics of the subject be excluded, for all of the data have to submit to precise definition and classification. Obviously, "Correlative Neuroanatomy" has been written for the medical student, or perhaps the young physician who is not a trained neurologist. If its purpose is to permit the hasty and transitory memorization of sufficient data to enable one to pass an examination, then it is not a failure. However, if the authors intended that their publication be used, in place of the several textbooks to which they refer so freely, for the purpose of really teaching fundamental neurology, they have not succeeded. It is in that essential lack of a dynamic approach that they fail. For it is only when one has a grasp of the dynamics of a subject, as the pathogenesis of a disease, that one knows the subject and does not have to memorize pre-arranged data. Actually the material contained in "Correlative Neuroanatomy" is readily available in standard texts, in which dynamics are given due consideration. If this condensation of neurology fails the medical student, it surely is of little value to the trained neurologist.

In addition to its general inadequacy, "Correlative Neuroanatomy" is not without some significant errors. Some of the latter may well be a result of the necessity to condense the material. A number of the inaccuracies will be pointed out. Under cranial nerve II various visual defects are listed, among them the entity, "optic agnosia—(word blindness)—cannot name objects seen—angular gyrus lesion." It is

hardly correct to classify an agnosia among the cranial nerve lesions, even though it is qualified by the reference to the angular gyrus. Actually "optic agnosia" and "word blindness" are not synonymous. On page 7 one finds the statement, "circumferential blindness ('tubular vision') due to hysteria or retrobulbar neuritis." Retrobulbar neuritis notoriously causes a central scotoma and not a constriction of the peripheral fields. Under cranial nerve VIII the authors include, "sensory aphasia—(word deafness)," and "auditory hallucinations" as "symptoms of VIII nerve involvement." Similarly, "motor aphasia" is incorrectly listed among the "symptoms and signs of vagal involvement," as are "psychogenic disturbances." The latter are also included under the cranial nerves XI and XII. Psychogenic disturbances, aphasia, and agnosia involve disturbances of the cerebral cortex, and not of the cranial nerves.

Since this text has been planned to be concise, why the authors pay so much attention to the antiquated terminology commemorating the many pioneers in neurology is hard to understand. Many of the names listed are rarely used. Would it not be best to discourage their employment by omitting them, and using more meaningful designations, even if longer? For instance, under progressive muscular atrophies, among the bulbar types a "Fazio-Londe" syndrome is referred to. Wilson in his encyclopediac text merely refers to these two authors among many others who have described cases of subacute bulbar palsies. Also, why is it necessary to refer to the resistance to stretching the brachial plexus in neuritis of the latter, as Bikel's sign?

While the definitions of many terms are well done, the thumb-nail descriptions of the various disease entities and tumors are hardly sufficient for the beginner, and surely unnecessary for the initiate.

Perhaps the reader harbors a peculiar bias against compendia that make available skeletal material that can be exploited by those who are disinclined to make a more thorough study of neurology, no doubt "Correlative Neuroanatomy," barring its errors, has served many a medical student well in helping him prepare for examination.

H. A. T.

*Obstetric Analgesia and Anesthesia.* By FRANKLIN F. SNYDER. 401 pages; 16 × 24 cm. W. B. Saunders Company, Philadelphia. 1949. Price, \$6.50.

From the author's rich background of clinical and experimental investigation comes this interesting compilation of data concerning the various agents used in obstetrics to produce analgesia and anesthesia. The analysis of the physiologic and pharmacologic factors together with the survey of clinical case reports and conclusions, seemed to the reviewer to be particularly unbiased.

The work is divided into two sections, the first of which, comprising about half of the book, is a rather technical but clear exposition of fetal respiratory physiology and pathology, which proposes to prove that the fetal respiratory system is the site of greatest vulnerability to injury that proves fatal during labor or following it. It is also shown that intrauterine respiratory activity, like that seen after birth, takes place. Thus, breathing begins far back in embryonic life. It is indicated that since the functional significance of fetal respiration has been established, a new approach is open to the analysis of the hazards of labor to the child. The author describes much of his own fundamental experimental work on fetal respiratory physiology including assay of the pharmacologic factor in labor as illustrated by the action of various drugs in obstetric analgesia. He uses fetal respiratory movements as a sensitive indicator which can detect the earliest effect of narcosis. Results are expressed in terms of depression in activity of the fetal respiratory system and by impairment in the effective uterine expulsive mechanism. The first section is a background for the more clinical second section.



In his introduction to the second section, the author states his belief that how much pain relief can be attained for the mother and how little risk is involved for the child, are matters that can hardly be settled by clinical impressions alone. Thus, in evaluating each analgesic or anesthetic agent, he determines its potency in the relief of pain, its effect upon the fetus and its effect upon the mother, especially upon the labor mechanism. In the chapter on regional anesthesia, the results of the use of various agents in the conduct of labor are presented from the standpoint of the method of administration rather than from that of the action of a given drug.

The book is attractively printed, serviceably bound, and an extensive bibliography is found at the end of each chapter. There is an excellent summary concluding most of the chapters. The illustrations are clear and well-chosen. There is an adequate index. To all who practice obstetrics, this book will be found most interesting and helpful.

J. E. S.

### BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Autobiography of Dr. Robert Meyer (1864-1947): A Short Abstract of a Long Life.*

With a Memoir of Dr. Meyer by EMIL NOVAK, M.D. 126 pages; 26 × 17.5 cm. 1949. Henry Schuman, New York. Price, \$2.50.

*Die Bazillenruhr.* By LUDWIG ROEMHELD. 125 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$3.25.

*Blakiston's New Gould Medical Dictionary: A modern comprehensive dictionary of the terms used in all branches of medicine and allied sciences, including medical physics and chemistry, dentistry, pharmacy, nursing, veterinary medicine, zoology and botany, as well as medicolegal terms; with illustrations and tables.* 1st Ed. Editors: HAROLD WELLINGTON JONES, M.D., NORMAND L. HOERR, M.D., and ARTHUR OSOL, Ph.D., with the coöperation of an Editorial Board and 80 contributors. 1294 pages; 25.5 × 17.5 cm. 1949. The Blakiston Company, Philadelphia. Price, \$8.50.

*Blood Transfusion.* By H. F. BREWER, RICHARD ELLIS, R. I. N. GREAVES, GEOFFREY KEYNES, F. W. MILLS, R. BODLEY SCOTT, ANTHONY TILL and LIONEL WHITBY; Edited by GEOFFREY KEYNES. 574 pages; 22.5 × 15 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$12.50.

*Bridges' Dietetics for the Clinician.* 5th Ed. Edited by HARRY J. JOHNSON, M.D., F.A.C.P., Formerly Assistant Clinical Professor of Medicine, New York Post Graduate Medical School, etc. 898 pages; 24 × 16 cm. 1949. Lea & Febiger, Philadelphia. Price, \$12.00.

*Darmbrand Enteritis Necroticans.* By K. HANSEN, E. JECKELN, J. JOCHIMS, A. LEZIUS, H. MEYER-BURGDORFF and F. SCHUTZ. 212 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$7.50.

*Diagnostische und Therapeutische Eingriffe des Internisten: Vorbereitung, Technik, Komplikationen und Gefahren.* By DR. MED. EBERHARD REGENBOGEN. 262 pages; 21 × 15 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$4.50.

*Differentialdiagnose der Inneren Medizin. 3. Unveränderte Auflage. Herausgegeben von Seinen Schülern.* By NÄGELI. 794 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$9.00.

- Einführung in die Innere Medizin.* By DR. HANS JULIUS WOLF. 608 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$7.25.
- Das Ekg-ABC: Eine Systematik zur Auswertung von Elektrokardiogrammen.* By MAX WALDHECKER. 114 pages; 21 × 14.5 cm. (paper-bound). 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$2.25.
- Die Erkrankungen des Darmes. Anhang: Die Prokto-sigmoidoskopie.* By WALTER ZWEIG (London). 253 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$6.75.
- Grundlagen zur Erforschung des Alterns.* By DR. PAUL MATZDORFF. 248 pages; 23.5 × 15.5 cm. 1948. Verlag von Dr. Dietrich Steinkopff, Frankfurt/Main, Germany. Price, DM 13.50.
- Die Insulin-lipodystrophie.* By PROF. DR. FERDINAND ADALBERT KEHRER. 50 pages; 21 × 14.5 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$1.50.
- Die Konstitutionellen Vergrosserungen Umschriebener Körperabschnitte.* By PROF. DR. FERDINAND ADALBERT KEHRER. 293 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$8.50.
- Lehrbuch der Haut- und Geschlechtskrankheiten.* By DR. WALTHER SCHÖNFELD. 467 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$7.25.
- Lehrbuch der Klinischen Hämatologie.* By PROFESSOR DR. HANS SCHULTEN. 499 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$11.00.
- Leitfaden der Blutmorphologie.* By LYDIA SCHUDEL. 47 pages; 24.5 × 17 cm. (paper-bound). 1947. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$3.00.
- Die Lungentuberkulose.* By PROF. DR. MED. H. GISSEL and DR. MED. HABIL. P. G. SCHMIDT. 264 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$8.00.
- Marihuana in Latin America: The Threat It Constitutes.* By PABLO OSVALDO WOLFF, M.D., Ph.D., M.A., Buenos Aires, Argentina, Member of Expert Committee on Habit Forming Drugs of the World Health Organization. 56 pages; 20.5 × 13.5 cm. (paper-bound). 1949. Sponsored by Washington Institute of Medicine; published by The Linacre Press, Inc., Washington, D. C. Price, \$1.50.
- Medizinische Klinik ein Fortbildungskurs für Ärzte.* By PROF. DR. FERDINAND HOFF. 467 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$9.00.
- Modern Practice in Psychological Medicine—1949.* Edited by J. R. REES, M.D. 488 pages; 25 × 17 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$10.00.
- Neuere Tuberkuloseforschung I.* By OBERMEDIZINALRAT DR. GRIESBACH, Augsburg. 112 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$2.00.
- Outlines of Internal Medicine.* 6th Ed., First Printing. Edited by C. J. WATSON, M.D., Head, Department of Medicine, University of Minnesota. First four

- parts of volume, 434 pages; fifth part of volume, 94 pages; 29 × 22 cm. 1949. William C. Brown Company, Dubuque, Iowa. Price, \$12.00.
- Die Pathologisch-anatomischen Grundlagen der Allergie.* By Doz. DR. MED. WILHELM EICKHOFF. 95 pages; 21 × 14.5 cm. (paper-bound). 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$2.50.
- Pathologische Physiologie der frischen, geschlossenen Hirnverletzung, insbesondere der Hirnerschütterung; klinische, anatomische und experimentelle Befunde.* By R. WANKE. 200 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$7.25.
- Rational Medicine.* By JOHN W. TODD, M.D. (Lond.), M.R.C.P. (Lond.), Assistant Physician to Farnam Hospital, etc. 378 pages; 22.5 × 14.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$6.50.
- Rehabilitation of the Handicapped: A Bibliography, 1940-1946* (in two volumes). By MAYA RIVIERE. Total pages in both volumes, 998; 24 × 15.5 cm. 1949. National Council on Rehabilitation, New York. Price, \$10.00.
- Rh-Syllabus.* By ALEXANDER S. WIENER, M.D., F.A.C.P., F.C.A.P. 28 pages; 21 × 14.5 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$0.75.
- Die Technik der Blutgruppen- und Blutfaktorenbestimmung.* By DR. MED. HABIL. PETER DAHR. 250 pages; 21 × 15 cm. (paper-bound). 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$3.75.
- Textbook of Medical Treatment.* 5th Ed. By Various Authors. Edited by D. M. DUNLOP, B.A. (Oxon.), M.D., F.R.C.P. (Edin.), F.R.C.P. (Lond.), Professor of Therapeutics and Clinical Medicine, University of Edinburgh, etc.; L. S. P. DAVIDSON, B.A. (Camb.), M.D., F.R.C.P. (Edin.), F.R.C.P. (Lond.), M.D. (Oslo), Physician, H.M. The King in Scotland, etc., and J. W. McNEE, D.S.O., D.Sc., M.D. (Glas.), F.R.C.P. (Edin.), F.R.C.P. (Lond.), Physician, H.M. The King in Scotland, etc. 999 pages; 24.5 × 17.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$8.50.
- A Textbook of Neuropathology, with Clinical, Anatomical and Technical Supplements.* By BEN W. LICHTENSTEIN, B.S., M.S., M.D., Associate Professor of Neurology, University of Illinois College of Medicine, etc. 474 pages; 25.5 × 16.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$9.50.
- Die Tuberkulose des Kindes: Ein Lehrbuch aus der Kinderheilstätte Wangen im Allgäu.* By DR. MED. HABIL. HEINRICH BRÜGGER, DR. MED. HABIL. REINER W. MÜLLER, and DR. MARIA BIRKENFELD. 340 pages; 24.5 × 17 cm. 1948. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$5.00.
- Tuberkuloselexikon für Ärzte und Behörden.* By DR. MED. HABIL. WILHELM ROLOFF. 372 pages; 19 × 12.5 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$4.50.
- Über Weichteiltuberkulose (Tuberculosis colliquativa profunda).* By DR. MED. MARIA BIRKENFELD. 45 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$2.00.
- Weitere Fortschritte in der Blutgerinnungslehre.* By PROF. DR. MED. KARL LENGGENHAGER. 243 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart; imported by Grune & Stratton, Inc., New York. Price, \$5.50.

# COLLEGE NEWS NOTES

## A.C.P. POSTGRADUATE COURSES

A schedule of the courses is repeated on the inside back cover page of this journal.

Although Course No. 1, CARDIOLOGY, at the National Institute of Cardiology of Mexico, had a registration of only twenty-five, due to the lateness of the announcement of the course, it was received with enthusiasm. Quoting from some of the reports received from those in attendance: "I spent a very profitable two weeks. The course was well-organized and well-conducted. I was very favorably impressed with the well-trained group of men there. The course gave me just what I wanted."—M.D., Tennessee. "In my opinion, it was the best course in Cardiology which it has been my privilege to attend. Its strong points were (1) the care with which the program was arranged; (2) the coordination between the Director and the heads of each department; and (3) the high level of instruction which each speaker maintained."—M.D., California. "A most profitable course and enjoyable vacation. The course is highly recommended, especially for catheterization technics and angiocardiology."—M.D., Texas. "The course was excellent beyond description. The courtesy of the staff and the zeal and interest of each participant has set a goal difficult to equal."—M.D., New York. "The program arranged by Dr. Chavez was informative and illuminating. Not only will the scientific program be forever remembered but likewise the hospitality of the Director. May I add that the enthusiasm and good fellowship displayed by Dr. George Morris Piersol, Dr. William Dock and Dr. George C. Griffith, American College of Physicians' guests, were deeply appreciated. I wish to express due thanks to The American College of Physicians for granting such opportunities to its members."—M.D., Pennsylvania.

When the course in Cardiology in Mexico is repeated, it is hoped that adequate notice of perhaps six or more months will be given to all members of the College, so that they can take advantage of this outstanding course.

Courses No. 2 and No. 3, GASTRO-ENTEROLOGY at the University of Chicago, and CLINICAL NEUROLOGY at Jefferson Medical College of Philadelphia; respectively, will have been concluded before the publication of this news item. In each case the registrations were reasonably large and representative. Reports from the men registered are not yet available, but from former experience it can be stated, with assurance, that no better courses in the respective fields could be arranged anywhere. Both courses have been given previously with signal success.

Those wishing to register for the remaining courses on the schedule should do so without further delay. Course No. 6, THE BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO INTERNAL MEDICINE, at the University of Wisconsin Medical School, is already registered to capacity and some of the other courses are approaching that point. Especially do Courses No. 7 and No. 8, BLOOD DYSCRASIAS, at the Medical College of Alabama, and THE PHYSIOLOGICAL APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES, at the University of Southern California School of Medicine, respectively, warrant increased registration, because there are still ample facilities available. Detailed outlines of all courses can be obtained from Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

---

## RESEARCH FELLOWSHIPS OF THE AMERICAN COLLEGE OF PHYSICIANS

Some months ago The American College of Physicians announced a limited number of Fellowships in Medicine and/or Pediatrics available from July 1, 1950

through June 30, 1951. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend varies from \$2,200 to \$3,200 per annum, according to circumstances.

In previous years, there has been a large number of applicants for these Fellowships. This year the number has greatly decreased.

Application forms may be obtained from the Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa. They must be submitted in duplicate by an early date in October. Announcement of awards will be made following the Board of Regents meeting on November 13, 1949.

---

#### A.C.P. COMMITTEES AND REGENTS MEET NOVEMBER 11-13, 1949

The regular Autumn meetings of the Board of Regents and their various committees will be held at the Headquarters of the College in Philadelphia, November 11-13, 1949. At this time Research Fellowships for 1950-51 will be awarded; the postgraduate program for 1950 will be adopted; candidates for membership, presented prior to September 12, 1949, will be passed on, and other essential business of the College transacted.

The next succeeding meeting of the Committee on Credentials for the consideration of candidates will be held at Philadelphia on or about March 19, 1950.

The next Annual Session of the College will be held at Boston, Mass., April 17-21, inclusive, 1950. General Headquarters, Mechanics Building; Hotel Headquarters, The Statler and Copley Plaza Hotels. All reservations will be handled through a Housing Bureau, conducted by the Boston Convention Bureau.

---

#### A.C.P. DIRECTORY, 1949

The new and revised Directory of The American College of Physicians is progressing toward completion; but the revisions were so extensive that the publication date has been delayed beyond that originally anticipated. It is confidently hoped that it will be mailed during November to those who placed orders. The pre-publication price was \$4.00. Members will be billed after delivery of their copy to them. For those who have not previously placed orders, the post-publication price is \$5.00.

---

Grateful acknowledgment is made of the receipt of the following publications from Fellows of the College:

"Dorothea Lynde Dix: America's Greatest Woman," Frederick R. Taylor, M.D., F.A.C.P., High Point, N. C.

"Three Suggestions for Medical Graduates," Paul F. Whitaker, M.D., F.A.C.P., Kinston, N. C.

---

#### POSTGRADUATE COURSE IN DISEASES OF THE CHEST

A Postgraduate Course in Diseases of the Chest is announced by the Council on Postgraduate Medical Education of the American College of Chest Physicians to be

held at the Hotel New Yorker, New York City, November 14-18, 1949. The announcement states that the course is given with the coöperation of members of the staffs of the New York City medical schools and hospitals. Fee for the course is \$50.00. Information can be obtained from the American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Ill.

---

#### POSTGRADUATE COURSE IN CARDIOLOGY AT DALLAS

A postgraduate course in Cardiology presented under the coöperation of the Dallas Academy of Internal Medicine, the Dallas Heart Association and the Faculty of Southwestern Medical School will be conducted at Dallas, November 28-December 1, 1949. The course will be held at the Melrose Hotel and Parkland Hospital. Applications for registration should be sent to the Dallas Southern Clinical Society, 433 Medical Arts Bldg., Dallas 1, Tex.

---

#### COURSE IN CLINICAL CYTOLOGY

McGill University and the Royal Victoria Hospital, Montreal, announce a two-weeks course in individual instruction in Cytological Technics and Interpretation, November 7-21, 1949, under the direction of Dr. J. Ernest Ayre. The tuition fee is \$100.00.

---

#### RESEARCH GRANTS AND FELLOWSHIPS TO BE MADE AVAILABLE IN 1950 BY THE LIFE INSURANCE MEDICAL RESEARCH FUND

Applications for 1950 grants in aid of research on cardiovascular problems will be received by the Life Insurance Medical Research Fund up to January 1, 1950. Support is available for physiological, biochemical, and pathological research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about \$550,000 will be awarded for these grants.

Applications for postgraduate fellowships for training in research in 1950-51 will also be received by this Fund up to January 1, 1950. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.) or the equivalent is required. The annual stipend varies, as a rule being between \$3,000 and \$4,000, with larger amounts in special cases. At least 12 postgraduate fellowships will be available.

New grants and fellowships will become available on July 1, 1950.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29, New York.

A number of pre-doctoral fellowships for basic training in research will also be awarded. Details are available on request.

---

#### FEDERAL GRANTS FOR NATIONWIDE ATTACK ON HEART DISEASE

The United States Public Health Service and the National Heart Institute recently announced grants of federal funds amounting to \$8,614,737 to 85 medical schools and research institutions in 34 states and the District of Columbia. Admin-

istered by the National Heart Institute of the Public Health Service, the funds will be used for stepped-up heart research, for expanded programs of heart teaching in medical schools, and for building additional heart research laboratories throughout the country.

---

#### MEDICAL SCHOOLS RECEIVE KELLOGG GRANTS

Grants for medical education amounting to nearly a quarter of a million dollars have been announced by the W. K. Kellogg foundation, the University of Oklahoma School of Medicine to receive \$130,000 over a period of five years and Emory University School of Medicine, Atlanta, to receive \$110,000. The grants are intended to help support certain programs which these medical schools have begun or will place in operation during the present academic year.

---

The Interstate Postgraduate Medical Association of North America will hold its Thirty-fourth International Medical Assembly at Philadelphia, October 31–November 3, inclusive, 1949, under the presidency of Dr. Evarts A. Graham, F.A.C.S., of St. Louis and the general chairmanship of Dr. Richard A. Kern, F.A.C.P., President of the Philadelphia County Medical Society and Professor and Head of the Department of Medicine, Temple University School of Medicine.

---

#### ANNUAL "HOME-COMING" AT POTTENGER SANATORIUM

For many years friends and former patients of Dr. Francis M. Pottenger, Sr., F.A.C.P., have gathered together on the Sanatorium grounds in Monrovia, Calif. for a "Home-Coming" to honor Dr. Pottenger. A special occasion this year, on September 25, was held to mark Dr. Pottenger's eightieth birthday. Dr. Pottenger was President of The American College of Physicians in 1932–33.

---

#### SEPARATE AIR FORCE MEDICAL DEPARTMENT ESTABLISHED

The Technical Information Branch of the Office of the Surgeon General, Department of the Air Force, announced during the latter part of August the establishment of a separate Air Force Medical Department. Reorganization of the Office of the Surgeon General, U. S. Air Force, has been completed and will no longer be under Army control. Major General Malcolm C. Grow is the Surgeon General. Major General Harry G. Armstrong, F.A.C.P., has been named Deputy; and Brigadier General Dan C. Ogle (A.C.P. Associate), is Special Assistant to The Surgeon General.

---

Dr. T. Grier Miller, F.A.C.P., Philadelphia, Pa., has been unanimously elected to the Advisory Board in Gastro-enterology of the American Board of Internal Medicine, succeeding Dr. Henry L. Bockus, F.A.C.P., Philadelphia, Pa., whose term has expired.

---

Dr. George E. Baker, F.A.C.P., Casper, Wyo., presided at the Rocky Mountain Medical Conference, Butte, Mont., July 31–August 1, 1949, and at the 46th Annual Meeting of the Wyoming State Medical Society at Casper, Wyo., September 12–14, 1949. Dr. Baker was President of the State Society.

Dr. Roscoe L. Pullen, F.A.C.P., Seattle, Wash., has been appointed Professor of Graduate Medicine, Director of the Division of Graduate Medicine, and Vice-Dean of Tulane University of Louisiana School of Medicine, New Orleans, effective October 1, 1949.

---

Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, has succeeded Dr. Hugh J. Morgan, F.A.C.P., Nashville, as a member of the American Board of Internal Medicine.

---

Dr. William Walter Hargrave, (MC), USN, F.A.C.P., retired from active duty in the Navy on October 1, 1949, with the rank of Commodore. His last duty assignment was that as Senior Medical Officer and Head of the Department of Hygiene at the U. S. Naval Academy, Annapolis. Dr. Hargrave is now the Health Officer for the Campbell-Charlotte Health District, Rustburg, Va.



## OBITUARIES

## DR. JORGE RODRIGUEZ MUNIZ

Dr. Jorge Rodriguez Muniz, F.A.C.P., Havana, Cuba, died of coronary disease May 21, 1949, at the age of 59. Dr. Muniz received his B.S. degree from the Institute of Havana in 1906. He graduated in medicine from the University of Havana School of Medicine, June 28, 1911. After his internship in Cova-donga Sanitarium, he entered medical practice for some time outside of Havana. In 1926, he joined the Department of Gastro-enterology of the Mount Sinai Hospital at New York where he worked first as a student in postgraduate courses in gastro-enterology and proctology and later as Instructor and Clinical Associate in the Postgraduate School. His teacher and good friend, Dr. Asher Winkelstein, once wrote about him: "His splendid personality, his unusual intelligence and his great ability, particularly in the field of proctology, together with a sympathetic attitude towards his patients, combine to make Dr. Muniz one of the most brilliant members of our Postgraduate School." He left the United States and many good friends in the Mount Sinai group and other centers and began to practice in Havana in the field of gastro-enterology and proctology in which he had been working until his death. Shortly after his return to Havana he was appointed proctologist and gastro-enterologist at the Freyre de Andrade Municipal Hospital which he served ever since. Dr. Muniz has published many articles in Cuba and in the United States, especially in relation to ulcerative colitis and other proctologic and gastro-enterologic topics.

He was a Fellow of the American College of Physicians (1941) and a member of the Cuban Society of Clinical Studies, the Societas Internationalis Gastro-enterologica, the National Gastro-enterological Association, the American Proctologic Society and the Cuban National Medical College.

In the course of years, Dr. Muniz established a very active practice in his field and in internal medicine. He always showed such an interest in the problems of his patients that he has left a great sense of loss among them. He was indeed a very fine and able physician who will always be remembered by all who knew him.

JOSÉ J. CENTURIÓN, M.D., F.A.C.P.,  
Governor for Cuba

## DR. FRANK HARRELL REDWOOD

Frank Harrell Redwood, M.D., F.A.C.P., a native of Virginia, died on May 27, 1949. Dr. Redwood was born at Suffolk, March 22, 1891, graduated from the Medical College of Virginia in 1913, interned in the Memorial Hospital, Richmond, in 1914, and did postgraduate work at the Presbyterian Hospital and the Neurological Institute, New York City, from 1916 to 1918. Subsequently Dr. Redwood served in the Medical Reserve Corps of the U. S. Army during World War I.

Returning to Virginia, Dr. Redwood became Attending Neurologist in the Norfolk General Hospital and the Hospital of St. Vincent de Paul, and Consulting Neurologist to the Memorial, Leigh, and U. S. Marine Hospitals. He became a Fellow of the American College of Physicians in 1935. He was a Former President of the Norfolk County Medical Society and a member of the American and Southern Medical Associations, The Medical Society of Virginia, the Association for Research in Nervous and Mental Diseases and the American Psychiatric Association.

# ANNALS OF INTERNAL MEDICINE

VOLUME 31

NOVEMBER, 1949

NUMBER 5

## THE ETIOLOGY OF RHEUMATIC FEVER\*

By HOMER F. SWIFT, M.D., *New York, N. Y.*

ALTHOUGH a causative rôle of streptococcal infections with respect to rheumatic fever is fairly widely accepted, the evidence for this opinion seems insufficient for the hypercritical. There are at least three attitudes concerning this question: (1) Acceptance of the thesis and a readiness to apply it practically to public health aspects of the problem; (2) Relative indifference to the information that has been laboriously collected and correlated; (3) Skepticism and reiteration of the statement that the cause of this disease is unknown, or claims that an unidentified virus is the offending agent. It is imprudent to belittle the rôle of a devil's advocate in any philosophical, political, or scientific discussion, for when he performs his task wisely, he will prevent proponents of a thesis from falling into errors, which may have serious and even fatal repercussions in the medical disciplines. It is important, nevertheless, not to allow his arguments to overwhelm the significance of careful observations and thus prevent their effective utilization. In current propaganda and appeals to the public for funds to support research in this disease, it is wise not to have assertions of our ignorance belittle the importance of well established data. Because these data may not appear simple in their relationships, there is danger that they may be ignored and their practical significance be neglected. The purpose of this lecture is to assemble various elements in the puzzle of the rheumatic fever problem and to arrange them in a satisfactory design, with the qualification that the nature of science is to grow and rearrange the elements forming its structure.

Probably the discovery of the action of salicylates in alleviating the toxic and painful manifestations of rheumatic fever materially hindered fundamental investigation of this disease. The symptomatic relief induced created a false sense of accomplishment; and not until several decades after

\* Kober Lecture, delivered at Georgetown University Medical Center, Washington, D. C., March 28, 1949.

Delivered in part before the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., April 1, 1949.

From the Hospital of The Rockefeller Institute for Medical Research, New York City.

this discovery had elapsed was it well demonstrated that the chronic heart disease, the real health menace of rheumatic fever, pursued its relentless course in spite of the relief of early symptoms afforded by salicylates.

The cost of rheumatic cardiac cripples far outweighs the expense in time, thought and money that have so far been applied to the prevention of the initiating disease. There are several convincing demonstrations that properly conducted prophylactic programs can be effective, but in so far as I am aware, few of the lessons in this field, learned just prior to or during the recent war, are being extensively applied or recommended in either military or civilian programs.

I am anticipating the thesis that a peculiar upper respiratory infection is important in the pathogenesis of this disease. Perusal of patients' histories almost two centuries old reveals descriptions of cases of acute articular rheumatism that followed closely in the wake of a severe sore throat. Probably the word "rheumatism" arose from the concept that a noxious humour "rheum" flowed from the inflamed throat to the joints; a concept not without merit today. Early in the last quarter of the 18th century, excellent clinicians reported that among some series of patients with acute articular rheumatism, at least 80 per cent had a preceding follicular tonsillitis within four days to four weeks of the onset of their rheumatism. During the succeeding 20 years there was much discussion concerning the significance of this sequential relationship; and at the end of the 19th century, Pribram,<sup>1</sup> in reviewing the literature on this subject, reported in different series of cases variations of from 1.7 to 80 per cent of recorded connection between the two diseases. Some clinicians also reported mild nasopharyngitis or otitis media as precursors of rheumatism.

Bacteriological studies did not resolve the differing opinions on this problem, for pneumococci, staphylococci, Pfeiffer's bacilli as well as streptococci were cultured from the sore throats, although the finding of streptococci outnumbered the others in frequency. Bacterially induced polyarthritis (somewhat resembling acute articular rheumatism) for example gonococcal or postdysenteric, confused the picture still more; and inability to distinguish hemolytic from nonhemolytic streptococci, the latter normal inhabitants of many human throats, left, at best, insecure ground for the proponents of a probable streptococcal causation of rheumatic polyarthritis.

The dilemma is well illustrated in the writings of Poynton and Paine,<sup>2</sup> who valiantly supported this thesis. Analysis of their bacteriological data indicates that in some cases they were dealing with *Streptococcus pyogenes* septicemia terminally complicating genuine rheumatic fever, and in others with subacute bacterial endocarditis superimposed on old rheumatic scarred valves. In their day, most observers regarded valvular endocarditis as being always induced by bacteria implanted on, or pressed into, the endothelial covering of the valves, a concept that has subsequently undergone considerable modification.

A forward step in streptococcal classification resulted from Schottmüller's blood agar plate technic for distinguishing hemolytic from nonhemolytic streptococci,<sup>3</sup> and the demonstration that the former comprised the more virulent strains. The frequent association of subacute bacterial endocarditis (endocarditis lenta) with chronic rheumatic valvular disease led many physicians to conclude that both conditions had as common causative agents the nonhemolytic streptococci which induced the finally fatal infection. This opinion was supported by the occasional post mortem recovery of viridans streptococci from the heart's blood of rheumatic subjects, for formerly bacteriologists little appreciated how rapidly, during the death agony or post mortem, green streptococci or enterococci may invade the blood stream from the mouth or intestines where they normally reside. Moreover, the temporary entrance into the blood of lowly virulent nonhemolytic streptococci following nose and throat operations, tooth extractions, instrumentation of the urethra or ureters, or manipulation of intensely inflamed pharyngeal tissues are phenomena, discovered in the past three decades, that explain the occasional recovery of green streptococci from the blood of rheumatic patients during life. It is, indeed, readily understandable how rheumatic fever-inducing properties were attributed to lowly virulent nonhemolytic streptococci, because the lesions they induce are usually nonpurulent, a characteristic of those of rheumatic fever; while in contrast, hemolytic streptococci are often pyogenic. Indeed, the impossibility of demonstrating pyogenic streptococci either in cultures of rheumatic exudates or proliferates, or microscopically in the visceral, articular, or subcutaneous lesions of rheumatic fever patient are features that could blind investigators to their potential pathogenic rôle in this disease. It appeared probable, moreover, that if the rheumatic lesions were invaded by streptococci, such lesions would more readily dispose of the easily phagocytatable viridans varieties than of the more virulent pyogenic hemolytic strains. Indeed we formerly attributed to the viridans streptococci a possible etiologic rôle in rheumatic fever, an opinion that now seems incorrect; but it stimulated animal experimentation and the study of the host-parasite relationships which eventually seem to have added to knowledge concerning this disease. Before discussing these experiments, it is advisable to orient ourselves concerning modern streptococcal bacteriology.

In the early 1920's the classification of streptococci was based mainly upon three general procedures: (1) determining their action on blood; (2) testing their ability to attack certain chemical substances of known composition which were added to artificial culture media; and (3) ascertaining their capacity to survive under critical chemical and thermal environments.<sup>4</sup> While identification on such biochemical bases is sometimes definitive, notably with *Streptococcus mastitidis*, *Streptococcus equi*, the enterococci and *Streptococcus lactis*, many other streptococci have several common biochemical capacities but different pathogenic potentialities; hence the resulting

confusion could not be easily resolved. This apparent chaos in the world of streptococci has largely disappeared, thanks in considerable measure to the discoveries of Lancefield<sup>5</sup> and her collaborators in our laboratories combined with those of Griffith<sup>6</sup> in London.

Recognition of the existence of at least 12 serologically recognizable groups (table 1) in addition to the ungrouped viridans varieties favored correlation of etiological relationships among certain streptococcal groups

TABLE I  
Serological Groups of Streptococci

Group	Common Name	Usual Habitat	Usual Pathogenicity
A	Human <i>Str. pyogenes</i>	Man	Many human diseases
B	<i>Str. agalactiae</i> ( <i>Str. mastitidis</i> )	Cattle	Mastitis
C	<i>Str. equi</i> Animal <i>Str. pyogenes</i> Human C <i>Str. dysgalactiae</i>	Horse Many animals Man and animals Cattle	Strangles Many animal diseases Respiratory and other infections Mastitis
E	Group E	Normal milk	None
F	Group F (minute)	Man	Slight; respiratory tract
G	Group G (minute) Group G (large colony)	Man Man Dogs	Upper respiratory tract Many areas Genital and respiratory tracts
H	Group H	Man	Questionable; respiratory tract
K	Group K	Man	Questionable; respiratory tract
L	Group L	Dogs	Genital tract
M	Group M	Dogs	Respiratory tract
D	Enterococci: <i>Str. faecalis</i> <i>Str. liquefaciens</i> <i>Str. zymogenes</i> <i>Str. durans</i>	Intestinal contents Man, many animals and dairy products	Gastro-urinary tract, gastro- intestinal tract, abscesses, heart valves, wounds, contaminated food poisoning
N	<i>Str. lactis</i> : <i>Str. lactis</i> <i>Str. cremoris</i>	Milk Cream	None None

or sub-groups and certain diseases of man, domestic and wild animals, fowls and insects, respectively. To elaborate upon this interesting and important topic at this point<sup>4</sup> would lead us too far from the subject of this communication; but the demonstration that approximately 95 per cent of streptococcal infections in man are caused by members of group A has favored a rational direction of attention towards phenomena connected with microorganisms belonging to this group.

## SOMATIC ANTIGENIC COMPONENTS

Groups are recognizable serologically because the strains within a group elaborate in common a group specific carbohydrate called C which gives a precipitin reaction in vitro when combined with its group specific antibody. Many groups are further divisible into serological types. The type specific components are sometimes polysaccharides, for example in group B, and sometimes, notably in group A, they are proteins which are designated type specific M substances.

The typing of group A streptococci stems primarily from the ability of a particular strain to induce in animals the ability to resist infection with that strain and also with other strains that elaborate a homologous type specific M protein. This resistance or type specific immunity may be actively induced by nonlethal infections, and also by parenteral injections of vaccines prepared from strains elaborating type specific M protein, but not from strains lacking this capacity. The serum of actively immunized animals

TABLE II

## Somatic Antigens of Group A Streptococci

Somatic Antigens	Antibodies	Specificity
C carbohydrate	Anti C precipitins	Group specific
Nucleoproteins	Antinucleoproteins	Common to many cocci
T proteins	Anti T agglutinins	Some type specific; some common to several types
M proteins . . . . .	Protective	Type specific
	Bacteriostatic	in vivo
	Anti M precipitins	in vitro
	Anti M agglutinins	in vitro*

\* With properly absorbed sera.

when injected in sufficient quantities into other animals protects them from infections with streptococci belonging to homologous types, but not from heterologous types.

Sera having this type specific protective capacity contain type specific antibodies. Of these, the most easily recognizable in vitro are anti M precipitins, which form precipitates after mixing suitable extracts of the streptococci in question with properly absorbed sera from highly immunized rabbits. Sera of men or animals infected with group A streptococci, or immunized with these bacteria, also contain agglutinins which may have type specific significance, provided accompanying non-type-specific agglutinins are suitably absorbed from the sera. This important proviso requires attention because many group A streptococci contain another somatic agglutigen, called T, that sometimes bears a close type relationship to an accompanying M protein, and at other times does not. For example, types 4, 24, 26, 28, 30 and 44 elaborate T antigens so closely related that on the basis of agglutination tests with unabsorbed sera no single one of these types

can be identified from the other, although each type elaborates an M protein specific for that respective type. Furthermore, the antibodies against the T antigen bear no close relationship to protective antibodies or to type specific immunity, a relationship easily demonstrated with anti M precipitins.

Another substance closely associated with type specific immunity to group A streptococcal infections is the so-called bacteriostatic antibody, that renders virulent non-phagocytatable streptococci liable to phagocytosis by leukocytes. In the direct bacteriostatic method complement, a thermolabile factor, and the leukocytes are contained in the blood of the individual being tested. If that blood contains the type specific bacteriostatic antibody, certain numbers of streptococci causing that patient's infection will be killed when mixed with the blood obtained shortly after venipuncture; if it does not, they will survive and grow on suitable media.<sup>7</sup> In the indirect method, complement, thermolabile factor and leukocytes are derived from the blood of a person presumably not previously infected with group A streptococci, and the bacteriostatic antibody in question is sought in the serum of the patient being considered. With this technic many sera obtained successively over long periods from the same patient and suitably preserved can be tested simultaneously, their antibody content measured quantitatively and its duration determined.<sup>8</sup> This test is quite type specific, and the bacteriostatic antibody detectable with it reflects a corresponding type specific resistance on the part of the patient who furnished the serum.

An interesting incidental observation has come from employing the blood of presumably normal adults to supply complement, thermolabile factor and leukocytes: these bloods, even without the addition of immune serum, may inhibit the growth of some strains of streptococci; and this phenomenon suggests that such bloods contain bacteriostatic antibodies stemming from previous streptococcal infections, which may have been either clinical or subclinical. This suggestion is further supported by observations that bacteriostatic antibodies rarely occur in the blood of quite young children, who probably have experienced few if any streptococcal infections. Furthermore a patient's serum obtained near the onset of a group A streptococcal infection practically never contains bacteriostatic antibodies specific for the streptococcal type that is inducing his latest infection; while most of these patients elaborate type specific antibodies against that type within a few weeks of infection, presumably due to type specific antigenic stimulation from his latest infection.

The bacteriostatic technic for studying antibody production by patients is the only in vitro test that gives results as strictly type specific as those furnished by passive protection of animals with immune sera, for both agglutination and precipitin tests with patients' sera often yield cross reactions with strains of other types. These non-type-specific reactions are partly attributable to the elaboration, by a patient infected with streptococci, of antibodies against several streptococcal somatic components or their metabolites, and partly to impure reagents. It is not yet possible to prepare streptococcal

extracts containing only M protein, for they usually contain residual antigenic substances that yield cross reactions with unabsorbed sera. In fact, suitable extracts prepared from group A hemolytic or viridans streptococci, pneumococci, or even staphylococci contain nucleoproteins which give cross complement fixation reactions with the sera of animals immunized with several varieties of streptococci, and with sera of patients suffering from subacute viridans streptococcal endocarditis, from acute group A streptococcal respiratory infections, or from pneumococcal pneumonia.<sup>9</sup> These results indicate that, in addition to the group or type specific components, the several members of the coccus family form somatic antigenic mosaics containing nucleoprotein-like substances with similar chemical configuration. Such phenomena point to the need for caution in interpreting the significance of both in vivo and in vitro tests performed with only partially purified streptococcal extracts.

### EXTRACELLULAR ANTIGENIC COMPONENTS

The serological reactions just discussed involve somatic antigens contained in streptococcal cells. Human subjects and animals while undergoing group A streptococcal infections or artificial immunizations, often form antibodies against extracellular products of streptococci. These extracellular antigens are elaborated into media nurturing these microorganisms and into the tissues of animals harboring them. Among the many extra-

TABLE III  
Extracellular Antigens of Group A Streptococci

Extracellular Antigens	Antibodies	Relative Antibody† Production in Human Infections	
		No RF	RF
Streptolysin O	Antistreptolysin O	++	+++
Streptolysin S	Antistreptolysin S	++	+
Streptokinase (Fibrinolysin)	Antistreptokinase	++	+++
Hyaluronidase (Types 4 and 24)	Antihyaluronidase	++±	++++
(Hyaluronidase precursor?)* all types			
Proteinase	Antiproteinase	(+)?	(+±)?
Desoxyribonuclease (Dornase)†	Anti-DORNase†	+	++
Ribonuclease	Antiribonuclease	?	?
Erythrogenic toxin	Antitoxin	?	?

\* The existence of a precursor is assumed because of the frequent stimulation of streptococcal antihyaluronidase following most group A streptococcal infections.

† The abbreviation DORN is derived from DesOxyRiboseNuclease (Tillett et al.).

‡ The designation "relative" refers to statistical analysis of groups of patients and not to one individual.

cellular antigens, those longest studied are erythrogenic toxins, streptolysin O, and fibrinolysin, more accurately designated streptokinase; others have more recently attracted attention.

It is now generally accepted that scarlet fever is caused by group A streptococci that elaborate a rash-inducing toxin against which the patient possesses no effective antitoxic immunity when infected. This toxin cir-



culates in his blood during the acute phase of scarlet fever, and stimulates the formation of antitoxins that accompany and probably effect recovery. Many people apparently develop these toxin-neutralizing antibodies without suffering from scarlet fever, but probably from infections with streptococcal strains that elaborate insufficient erythrogenic toxin to induce a rash but still enough to induce the production of antitoxin. Once having developed this antitoxic immunity, most persons retain it the rest of their lives; hence they may subsequently undergo severe infections with erythrogenic toxin-producing streptococci without developing a rash. The erythrogenic toxin is probably not involved directly in the pathogenesis of rheumatic fever; but scarlet fever, being a group A streptococcal disease, is consequently a frequent precursor of rheumatic fever; hence the old designation "scarlatinal rheumatism" has nosological significance mainly because it supports the thesis that group A streptococcal infections induce rheumatic fever.

Streptolysin O is an extracellular hemolysin elaborated by most strains of group A streptococci and a few strains of groups C and G. An antibody, designated antistreptolysin O, which neutralizes its hemolytic properties *in vitro*, occurs in the sera of animals following injections with large amounts of cell-free streptolysin, or after suitable streptococcal infections.<sup>10</sup> It also often appears and usually increases progressively in strength in the sera of patients recovering from group A streptococcal infections<sup>11</sup> provided the infecting strains elaborate this lysin. When they do not, a patient elaborates no antistreptolysin O in his serum. Some patients, however, even though infected with hemolysin-O-producing strains fail to develop antistreptolysin O. A rising titer of this antibody after an infection is strong presumptive proof of its group A streptococcal etiology. Such antibody production, frequently observed in rheumatic fever patients, has furnished very convincing evidence that group A streptococcal infections are precursors of their rheumatic attacks. That this test is not specific with respect to rheumatic fever, but only to the precursory streptococcal disease, should be emphasized, and also that a negative test does not eliminate the possibility of such a streptococcal precursory infection.

Streptokinase, a component of streptococcal fibrinolysin,<sup>12</sup> is also found in media supporting growth of many streptococci belonging to group A, to some of groups C and G, and rarely to group B. It activates a precursor, plasminogen, present in most human sera, to form plasmin, an active fibrinolytic agent.<sup>13</sup> Patients infected with streptokinase-producing streptococci elaborate an antibody called antistreptokinase (formerly antifibrinolysin) which is quantitatively measurable in test tubes.<sup>14</sup> A *rising* titer of this antibody in the sera of rheumatic patients has significance comparable with that of antistreptolysin O: viz., it indicates a recent group A streptococcal infection; but a continually high titer may occur and be the result of infections many months previously.

Other antigenic and/or enzymatic substances elaborated into their nu-

tritional environment by group A streptococci and their respective antibodies require consideration.

Hyaluronic acid, hyaluronidase and antihyaluronidase have recently attracted considerable attention with respect to a possible pathogenic relationship in rheumatic fever. This acid, a highly viscid polysaccharide, makes up the capsules formed by many streptococci belonging to groups A and C.<sup>15</sup> Its presence bears close relationship to the virulence of "animal" group C streptococci,<sup>16</sup> but it has only slight significance in the virulence of group A strains.<sup>17, 18</sup> Hyaluronic acid is widespread in the bodies of vertebrates, notably in the umbilical cord, vitreous humor, synovial fluid, and in the interfibrillar cement substance of collagen.<sup>15</sup> Enzymes that split it are designated hyaluronidases, and several have been described from different sources: leech heads, mammalian testicular extracts, groups A and C streptococci, pneumococci, staphylococci and clostridia. While the common action of the enzymes from these different sources is to split any hyaluronic acid into less complex and viscid products, each hyaluronidase appears to be antigenically specific according to its respective origin; e.g., antihyaluronidase in the serum of persons infected with group A streptococci does not react with hyaluronidase from other bacteria. Three technics for demonstrating hyaluronidase have been employed: mucin clot solution; turbidity reduction; and as a spreading factor (Duran-Reynals<sup>19</sup>). Antibodies against hyaluronidases are measured by their ability to prevent these actions. With the mucin clot prevention technic and a substrate from umbilical cords, hyaluronidase production has been demonstrable only with type 4 and type 22 group A streptococci<sup>20</sup>; but Pike,<sup>21, 22</sup> employing the turbidity reduction technic with hyaluronic acid from streptococcal capsules, found hyaluronidase production by over half of his noncapsulated group A strains and even by some capsulated strains. The possibility that most group A strains form this enzyme, usually as a precursor must be entertained, for although it is difficult of demonstration *in vitro*, the fact that most patients infected with group A streptococci elaborate streptococcal antihyaluronidase indicates its widespread occurrence in these microorganisms. The degree of this antibody response, moreover, suggests that hyaluronidase is a very strong antigen, possibly the strongest of the extracellular antigens.

New born babies have practically the same streptococcal antihyaluronidase content in their sera as is present in that of their mothers; but this disappears within six months. Beginning in the three to five year age period, this antibody begins to appear with a slowly increasing frequency, until the age group of 20 years. The relative frequency curve then remains constant until the 60 year age group, when it falls slightly.<sup>23, 24</sup> This phenomenon, and the demonstration of antibodies against erythrogenic toxin slowly increasing with age, reflect roughly the occurrence of group A streptococcal infections in a considerable portion of the population.

The other three extracellular enzymes, proteinase,<sup>25</sup> desoxyribonuclease and ribonuclease,<sup>26</sup> have been much less studied with respect to different human infections; but it has been shown that antibodies are formed against the latter two by patients suffering from group A streptococcal infections both with and without subsequent rheumatic fever<sup>26</sup>; and by animals against the former.<sup>27</sup> These enzymes are probably relatively weaker antigens than hyaluronidase, streptolysin O and streptokinase. McCarty has pointed out that all of these streptococcal extracellular antigenic enzymes have functions comparable to the digestive enzymes found in the gastrointestinal tracts of vertebrates; and, in that they break down more complex molecules into simpler ones, they probably make available to the bacteria nutriment occurring in the media in which the microorganisms grow.

Streptolysin S, discovered by Todd<sup>28</sup> is apparently the most toxic in vitro of any of the known extracellular streptococcal antigens. Bernheimer<sup>29</sup> has recently defined quite minutely the cultural conditions under which it is most readily produced; hence it should be possible to investigate more readily than formerly the disease conditions and immunological states under which anti-streptolysin S formation occurs. Studies already made on this subject are mentioned later.

The foregoing brief review of the somatic and extracellular antigens of group A streptococci and of their respective antibodies is requisite to a description of how these data have been applied in supporting the theory that members of this streptococcal group play an important rôle in the etiology of rheumatic fever.

#### SEQUENTIAL RELATIONSHIP BETWEEN GROUP A STREPTOCOCCAL INFECTIONS AND RHEUMATIC FEVER

About two decades ago, Coburn<sup>30</sup> in this country and Sheldon<sup>31</sup> and Schlesinger<sup>32</sup> in England almost simultaneously redirected medical attention toward the probable rôle of streptococcal respiratory infections as precursors of rheumatic fever, both in first attacks and in recurrences. The studies of Griffith,<sup>33, 34</sup> and his collaborators in England, of streptococcal epidemics in barracks, boy's schools and in fever hospitals indicated that single epidemics were usually due to one type of streptococcus, and that different types were active in successive school terms. With Lancefield's technics for identifying streptococcal groups it has been demonstrated that all of the respiratory infections that preceded attacks of rheumatic fever are caused by group A streptococci. This unique sequential relationship has been firmly established by many observers, particularly during the recent war in training areas where various respiratory infections were rife, and where cases of streptococcal nasopharyngitis, tonsillitis, and scarlet fever occurred by the thousands. Furthermore, bacteriological technics and good clinical observations have established quite definitely that respiratory infections due to microorganisms other than group A streptococci are not precursors of rheumatic fever.

Carefully gathered data moreover have demonstrated that the precursory streptococcal infection may be so mild as to escape clinical detection. For example, Kuttner and Krumwiede<sup>35</sup> showed that during epidemics in a closed institution, streptococci appeared for a few days in the nasopharynges of some children, who then sometimes had slight leukocytosis, and subsequently developed in their sera increasing titers of antistreptolysin O. Others have confirmed this observation under epidemic conditions. Thus was explained the old observation that rheumatic fever occurs at times without an obvious nasopharyngitis as a forerunner: it may be too mild for accurate clinical detection.

#### REACTIONS IN PATIENTS' SERA WITH EXTRACELLULAR STREPTOCOCCAL ANTIGENS

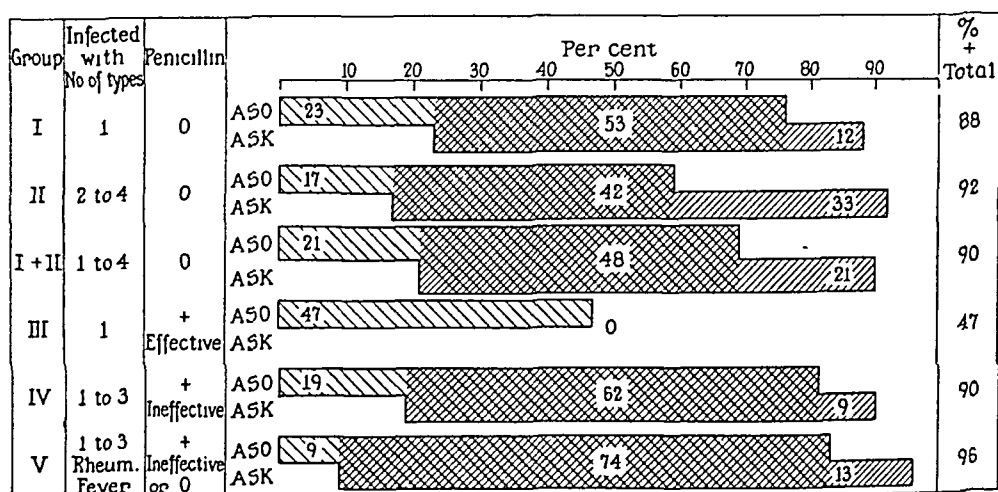
The streptococci inducing the precursory infection, moreover, disappear from the nose and throat before the onset of the rheumatism in a quarter to a third of the patients; hence other evidence of the precursory streptococcal activity is requisite; and the need has been supplied mostly by study of antibodies against the extracellular antigens of group A streptococci. Among these the antistreptolysin O test, devised by Todd,<sup>10</sup> has been most extensively employed; and with it between 80 and 90 per cent of rheumatic fever patients have been shown to develop abnormal amounts of antistreptolysin O in their sera. This is also true of most patients infected with group A streptococci; hence, this reaction is not diagnostic of rheumatic fever, but of group A streptococcal infections. That such infections may occur without inducing antistreptolysin O formation has already been noted; hence this test has only relative, not absolute value.

The application of technic for detecting antifibrinolysin,<sup>12</sup> and more recently for titering antistreptokinase quantitatively,<sup>14</sup> has still further confirmed the nature of the precursory respiratory infection, for sometimes there is an increase in antistreptokinase but no rise in antistreptolysin O, and vice versa. Several observers have reported a relatively higher content of these two antibodies in rheumatic than in non-rheumatic subjects, without having information concerning the antigenic composition of the streptococci infecting their patients; hence it was not known definitely whether the relatively greater antibody formation by the rheumatic group was due to differences in the parasites' activities or in the hosts' responses.

This question is apparently answered by the observations of Anderson, Kunkel, and McCarty<sup>36</sup> in a study of an epidemic in patients infected with strains of one or more of three different types of group A streptococci; so the antigenic stimulus was probably similar. Although, as in all such studies, there was marked variation among individuals, the group which had rheumatic sequelae developed distinctly more antistreptolysin O and antistreptokinase than did those who remained free of rheumatism. Other noteworthy observations were recorded: (1) those patients effectively treated

early with penicillin, who did not suffer rheumatic fever sequelae elaborated the smallest average amounts of these two antibodies, in fact, no detectable antistreptokinase; (2) in spite of low titers of these antibodies in this non-rheumatic group, the gamma globulin in their sera was significantly increased, an indication that other antibodies were probably formed; and (3) the average amounts of gamma globulin and antistreptolysin O were higher in the rheumatic fever group at the onset of their precursory streptococcal infections than in the non-rheumatic group. Hypothetically, this suggests that residual influences of previous group A streptococcal infections were more prominent or more durable in the rheumatic group than in the non-rheumatic, and that these residual influences may have "attuned" their tissues in the direction of a peculiar response to their latest streptococcal infection.

Antistreptolysin O and antistreptokinase production  
by different patients infected with same types of Group A streptococci



Anderson, Kunkel, and McCarty

CHART 1.

Finally, these authors' observations, summarized in chart 1 indicate the advantage of applying more than one serological test when searching for antistreptococcal antibodies; and the negative findings emphasize the hazard of denying the existence of a streptococcal infection in a patient because a particular antibody cannot be found in his serum.

The relatively stronger concentrations of antihyaluronidase recorded by Friou and Wenner,<sup>37</sup> Quinn,<sup>38</sup> and Harris et al.,<sup>39</sup> have suggested that the hyaluronidase of group A streptococci might be playing a special rôle in the production of lesions of collagen of which hyaluronic acid forms a considerable portion. That such a mechanism is possible cannot be categorically denied; but if it is an important factor in the induction of rheumatic lesions, it would seem that the microorganisms producing the most hyaluronidase would be the most liable to induce rheumatic fever. This, however, is con-

trary to experience: although it has been demonstrated that among group A streptococci only types 4 and 22 produce hyaluronidase in amounts sufficient to be easily detected in vitro, nevertheless, in at least two epidemics caused by type 4 streptococci in rheumatic subjects, no rheumatic recurrences were induced, while rheumatic fever frequently follows infections with streptococci that produce relatively little hyaluronidase. Furthermore, group C streptococci, quite frequent producers of considerable amounts of hyaluronidase, have likewise not been observed to induce rheumatic fever; and pneumococci, staphylococci and clostridia, also potent producers of this enzyme, are conspicuously negative as inducers of rheumatic fever.

The report by Guerra<sup>40</sup> that hyaluronidase (probably in testicular extracts) acted as a spreading agent (Duran-Reynals<sup>19</sup>) more powerfully in rheumatic fever subjects than in non-rheumatics, and that this spreading action is inhibited in guinea pigs by salicylates, has also excited renewed interest in the possible hyaluronidase-antihyaluronidase question with respect to rheumatic fever. Harris and Friedman<sup>41</sup> employing relatively weaker concentrations of streptococcal hyaluronidase were unable to demonstrate any unusual susceptibility to this spreading factor in rheumatic fever subjects compared with non-rheumatics. They suggest that the differences in their results from Guerra's were due to the strong irritating effects of the extracts used by the latter, and that these nonspecific effects might easily lead to misinterpretation of the results he observed.

Until more light is thrown on the whole hyaluronidase subject, it seems well to assume that the relatively more marked antihyaluronidase formation by rheumatic fever patients, compared with that of patients with simple streptococcal infections, is a concomitant rather than a causal phenomenon with respect to rheumatic fever.

The question of antistreptolysin S production by rheumatic fever patients has received relatively little attention, probably because of technical difficulties in producing this antigen for in vitro studies. Todd, Coburn and Hill<sup>42</sup> reported that antistreptolysin S was more abundant in the sera of patients suffering from simple group A streptococcal infections than in that of patients with rheumatic sequelae, even though the latter contained more than was found in normal persons' sera. With better methods for preparing streptolysin S, reported by Bernheimer,<sup>29</sup> investigations of the relationship of this lysin to various manifestations of streptococcal infections will probably be resumed.

The occurrence in a patient's serum of antibodies against the extracellular components of group A streptococci merely indicates a previous infection with some strain belonging to this group, but has no significance with respect to any particular strain or type. Furthermore, the finding of abnormal concentrations in a single serum is not definitely indicative of a recent streptococcal infection, because fairly high titers of antistreptolysin O, anti-streptokinase, or streptococcal antihyaluronidase may persist in a patient's serum for many months, possibly years, after a streptococcal infection. If

the titer is doubled or tripled in two or more sera successively obtained within a few weeks after an infection, however, a group A streptococcal causation of that infection is indicated.

### REACTIONS IN PATIENTS' SERA WITH TYPE SPECIFIC GROUP A STREPTOCOCCAL ANTIGENS

Theoretically the development of antibodies against the somatic component M of group A streptococci should furnish fairly conclusive proof of infection of a patient by a strain belonging to the particular type from which M was derived. This question has been much less studied in patients than has the production of antibodies against the extracellular antigens; but for a period of four or five years there was carried out in our laboratories and clinic a comparative study of the development, by streptococci-infected patients, of antibodies against the type specific M component of the streptococci with which the respective patients were infected.<sup>43</sup> Some of the results are shown in table 4.

TABLE IV  
Comparative Formation of Antibodies Against Group A Streptococcal Extracellular and Somatic Antigens, by the Same Group of Patients

Nature of Group A Streptococcal Infection	Uncomplicated	Complicated	With Rheumatic Fever Sequelae*	Total
Antibodies against extracellular antigens:				
Antistreptolysin O increase	69.7%	75.0%	85.3%	77.1%
Average beginning of rise	2.4 wks.	2.3 wks.	2.0 wks.	2.4 wks.
Antifibrinolysin increase	62.9%	80.0%	80.9%	73.0%
Average beginning of rise	3.1 wks.	2.5 wks.	2.3 wks.	2.6 wks.
Antibodies against somatic antigens:				
Bacteriostatic antibody increase	66.7%	68.8%	87.9%	75.6%
Average beginning of rise	4.2 wks.	3.9 wks.	6.1 wks.	5.1 wks.
Range	2-10 wks.	2-8 wks.	1-13 wks.	
Precipitin reactions with M extracts				
(a) Homologous type	45.5%	56.2%	85.3%	63.9%
(b) Heterologous type	33.3%	43.8%	61.8%	46.9%
Average beginning of rise	3.6 wks.	2.6 wks.	6.0 wks.	4.8 wks.
Range	1-8 wks.	1-5 wks.	1-23 wks.	

\* 12% of rheumatic patients also had purulent complications (see reference 43).

This table summarizes the relative development at weekly intervals of antibodies against two extracellular antigens and two somatic antigens by a fairly large group of patients, who were divided into three subgroups: (a) those without complications or sequelae; (b) those with purulent complications; (c) those with rheumatic fever sequelae (but four of the latter also had purulent complications). It was not possible to measure an antifibrinolysin increase in some of the patients because of high concentrations of this antibody in their sera at the onset of their latest streptococcal infec-

tions, and the quantitative antistreptokinase test was not yet available; but a study of the comparative development of the other three antibodies was possible. The rheumatic fever group developed relatively average higher antibodies than did the non-rheumatic group when tested with these four different technics. Although the average measurable antibodies against the extracellular antigens appeared at practically the same time following infection in all groups of patients, there was an average delay of approximately two to three weeks in the appearance of antibodies against the somatic antigens among the rheumatic fever group as compared with the non-rheumatic; this is illustrated in the bacteriostatic and anti M precipitin tests, and confirms earlier less extensive studies.<sup>44, 45</sup> The possible significance of this delay in the pathogenesis of rheumatic fever is not as yet evident.

Chart 2, summarizing graphically the antibody production by a comparable series of our patients indicates that the more tests that are applied to the same lot of sera, the more convincing is the evidence of a previous recent

Distribution of 4 different antibodies  
in 83 patients infected with Group A streptococci

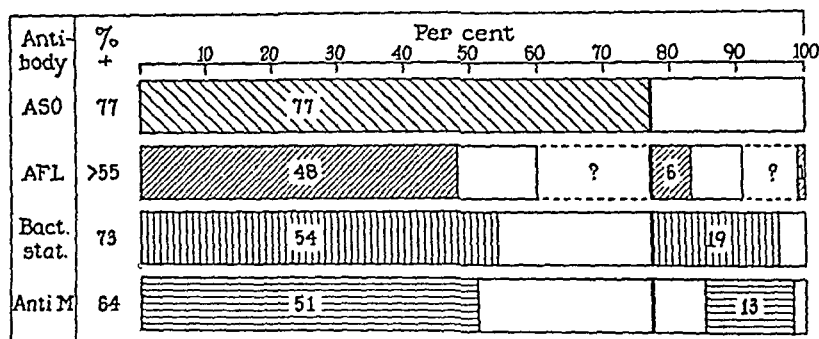


CHART 2.

streptococcal infection. Among patients undergoing 83 different group A infections, whose sera were repeatedly tested for antistreptolysin O, antifibrinolysin, bacteriostatic and anti M precipitin reactions, it was found that the first appeared in practically three-fourths of the cases; but among the patients' sera containing no antistreptolysin O, there was nevertheless a demonstrable formation of antifibrinolysin, bacteriostatic antibodies, or anti M precipitins; hence application of four tests indicates there was antibody formation against one or more streptococcal antigenic components in all instances.

A detailed analysis of this entire series of patients in whom it was possible to initiate the investigations very near the time of onset of their streptococcal infections and to continue them through the period when rheumatic sequelae were apt to occur, and in the event of the appearance of these sequelae for several months and sometimes for two or three years, showed the following: at the onset of an infection with a given type of group A streptococci, a patient's serum contained no bacteriostatic antibodies against that type, al-



though it often contained abnormal amounts of antistreptolysin O or antistreptolysin, and sometimes of bacteriostatic antibodies against streptococci belonging to types heterologous to that recently infecting a patient. This indicated that streptococcal infections had existed in that respective patient prior to the most recent infection. The type specific bacteriostatic antibodies usually appeared later in the course of infection or with recovery, and at times persisted for months or years, though occasionally they were demonstrable for only a few months. They were probably an index of type specific immunity. Bacteriostatic antibodies against heterologous types found very early in an infection probably indicate previous infections with streptococci belonging to these respective types.

#### MULTIPLE GROUP A STREPTOCOCCAL INFECTIONS IN ONE PERSON

A reorientation of our attitude towards human streptococcal infections has been brought about by the demonstration that most of them are caused by members of group A, and that this group comprises many immunologically recognizable types, of which about 40 have been identified with serological technics. Infection with one type leads fairly quickly to a specific immune resistance to that type, which, we may infer from data furnished by bacteriostatic tests, may persist for long periods. This inference is supported by experiments with monkeys that were rendered type specifically resistant to the homologous type of streptococci with which they were inoculated intranasally, but not to heterologous types.<sup>46</sup> In fact, type specific immunity in man does not insure resistance to other types, for there are numerous reports of superinfections of patients with streptococci heterologous in type from the original infecting strain. These superinfections frequently bring about complications, so that a patient may be simultaneously suffering from two different group A streptococcal infections. The possibility of cross- or superinfection indicates that, ideally, quarantine of patients should be based on the type that is infecting them,<sup>47</sup> an ideal rarely attained. Indeed, the rapidity with which streptococci can be made to disappear from the nasopharynx of a patient by intensive penicillin therapy, and the resistance to infection or to reinfection of persons receiving either sulfonamides or penicillin, make it easy to prevent the spread of streptococcal infections in families, schools, or other institutions (Massell et al. <sup>48</sup>).

For our present purposes, the phenomenon to be emphasized is the possibility, even probability, that one person may suffer several group A streptococcal infections during his life. This is indicated in many people by the following: a history of several different diseases usually caused by group A streptococci; the existence of immunity to streptococcal erythrogenic toxin, an immunity that increases roughly proportionally to age; the presence in many persons' blood of streptococcal antihyaluronidase, antistreptolysin O or antistreptokinase; the presence of bacteriostatic antibodies to several streptococcal types in the sera of many youths and young adults; and finally by the

demonstration that in one person suffering from repeated respiratory streptococcal infections, each attack has been induced by a group A streptococcus different in type from those shown to have caused previous attacks. This leads directly to the concept that in many people suffering from successive streptococcal infections, each infection is probably induced by group A streptococci different in type from those that caused prior infections in that person.

The varieties of nosologically definable diseases induced in human beings by group A streptococci are probably more numerous than is the case with any other microorganism. None of them, e.g., erysipelas or scarlet fever, is caused exclusively by a single serological type of streptococcus. The characteristic rash of scarlet fever is a peculiar response to an erythrogenic toxin elaborated by strains belonging to several types. Surgical or obstetrical streptococcal infections owe their peculiarity in part to the body areas invaded by the microorganisms, and in part to their virulence. In a streptococcal epidemic due to a single strain, such as occurs in milk-borne infections, and in families, institutions and barracks, many different clinical manifestations are observed; and this suggests that variations in the tissues of different persons are factors which help to condition the clinical pictures.

Powers and Boisvert<sup>49</sup> have outlined the changing types of response to streptococcal infections of the respiratory tract encountered at various age periods. In the very young, the symptoms are least clear cut; the nasopharyngitis is diffuse, of several weeks' duration, and prone to spread to the accessory sinuses and middle ears. The picture may be so noncharacteristic that its etiology can only be determined bacteriologically. Not uncommon is eczematoid dermatitis or vaginitis due to the same streptococci that are inducing upper respiratory infection. In school children, the nasopharyngeal response is somewhat more circumscribed and intense, the general symptomatology more stormy, the duration of a single infection shorter than in the very young. At the end of the first and in the second decade, especially after puberty, the course is usually still more acute, the fever higher, the duration shorter, the nasopharyngeal response more focalized and intense. Such turbulent and relatively brief acute courses exemplified by an attack of tonsillitis, are common in the third and fourth decades of life; and after 40, streptococcal respiratory infections are relatively much rarer than in the earlier age periods, which suggests that with advancing age a fairly effective immunity has developed.

Because these trends of streptococcal diseases towards localization resemble comparable phenomena seen in tuberculosis, Powers has designated the whole group of streptococcal diseases, "streptococcosis." It seems to me that because of the multiplicity of their clinical manifestations they may be more usefully compared with those of syphilis. This disease is currently so modified by antibiotics and other drugs that its normal evolution is difficult to observe.

In untreated or poorly treated syphilitic patients, the first response at the site of inoculation is a hard chancre, which is followed within a few weeks by

"spirochetemia." Then with intervening symptom-free periods, there occur successively the following manifestations: (1) widespread adenopathy and a diffusely generalized roseola involving most of the skin and visible mucous membranes; (2) finely papular syphilides, somewhat indurated, which tend to be grouped and to involve relatively less of the total integument than did the roseola; (3) larger syphilides more definitely grouped, fewer and of somewhat longer duration than those occurring previously; (4) comparatively late relapsing syphilides that are still larger grouped nodules, but often few in number. About the middle of the third year the lesions are large nodules or gummata, few in number, which may involve any tissue or any viscus. This changing character of the syphilides is attributable to a progressive retuning ("umstimmung") in the responses of the tissues in a body that is continually harboring *Treponema pallidum*. It is usually so well patterned that an experienced syphilologist can approximate fairly accurately the duration of a patient's syphilis from the character of his syphilides. Similar, but fewer clinical manifestations attributable to a somewhat comparable retuning of the tissues towards tubercle bacilli or tuberculin are seen in tuberculosis. Noteworthy is the granulomatous character of the lesions occurring in the tissues of a subject with such subacute or chronic infections.

The changing picture of streptococcal infections observed successively in infants, toddlers, school children, youths, and adults might well be conditioned by a comparable retuning of the patients' bodies to group A streptococci as the patients undergo repeated streptococcal infections, a retuning which results in a progressively increasing ability to focalize or limit the infections. While in the untreated syphilitic, the several relapses are all responses to infection with the one strain of spirochetes with which he was originally infected, this, as previously noted, is not true in one person with successive group A streptococcal infections, for many different serological types may, and probably do, infect one person; hence each infection constitutes a new disease in a body retuned, as a result of previous infections, to respond somewhat differently to his latest infection than to his former ones. After reaching the tertiary stage in syphilis the relapses are practically always gummatous; likewise, after a certain number of streptococcal infections the localized clinical responses tend to resemble one another even though the infecting strains belong to different serological types. In spite of their differences with respect to their M antigenicity, group A streptococci nevertheless have, in common, many other antigenic components which may stimulate the patients' tissues to a progressive retuning.

#### EXPERIMENTAL STREPTOCOCCAL INFECTIONS

A valid criticism of the thesis that group A streptococci play a unique rôle in the etiology of rheumatic fever stems from a failure of investigators consistently to induce in lower animals, infected with these streptococci, lesions closely resembling those of human rheumatic fever. For many years

this has been one of the objectives of experiments in our laboratories; and while there were many failures in attaining the primary objective, still much information was obtained which, with simultaneous studies of streptococcal infections in rheumatic patients, has apparently advanced our conception as to how streptococci may act to induce this disease. The pertinent data deriving from those investigations follow.

The earlier researches were carried out with rabbits infected intracutaneously with viridans streptococci. By employing suitable strains, it was shown that after the primary inflammatory response had subsided there often appeared, at the sites of the original inoculations, secondary reactions lasting for one to five days.<sup>50</sup> These reactions resembled somewhat those described by Koch in guinea pigs infected with tubercle bacilli, and in many respects differed from the Arthus phenomenon in rabbits injected with foreign serum.<sup>51</sup> This state of bacterial hyperreactivity could be distinctly increased and prolonged by repeated minute focal inocula of the streptococci. Indeed, it seemed to derive, to a considerable degree, from inflammatory foci, for when comparable doses of the same lowly virulent streptococci were injected intravenously into rabbits the focal responses to subsequent intracutaneous inoculation were less marked than in normal controls; in other words a state of immune hyporeactivity had been induced. It was next shown that by injecting lowly virulent strains of hemolytic streptococci, or heat-killed cultures, the state of hyperreactivity was induced by intracutaneous inoculation and a state of immune hyporeactivity by intravenous injections.<sup>52</sup> It was then found that although rabbits immunized intravenously with a strain of viridans streptococci developed a state of immune hyporeactivity to intracutaneous challenge with that strain, their response to a simultaneous challenge with a group A or a group C strain was that of hyperreactivity.<sup>53, 54</sup> Also noteworthy was the observation that two or three months after stopping the intravenous immunization, there developed a state of hyperreactivity to challenge with the immunizing strain.<sup>54</sup> Subsequently, when the significance of successive human infections with several different serological types of group A streptococci was appreciated, it was shown that prolonged intravenous immunization of rabbits with one type of group A streptococci or repeated intracutaneous infections with one fairly virulent type, usually induced the animals' tissues to respond subsequently to suitably sized intracutaneous inocula as follows: immune hyporeactivity to challenge with homologous type strains; and frequently, though not always, the same animals showed cutaneous hyperreactivity to inoculation with heterologous type strains.<sup>55</sup>

#### RHEUMATIC FEVER-LIKE CARDITIS FOLLOWING SUCCESSIVE INFECTIONS WITH DIFFERENT TYPES OF GROUP A STREPTOCOCCI

The probable import of one person having several streptococcal upper respiratory tract infections each with a different type of group A streptococci was at that time becoming increasingly insistent, for it seemed that with each

successive infection the patient's tissues were probably becoming retuned in a manner comparable to that observed in rabbits. It was, therefore, decided to test the effect of several successive inoculations of rabbits, each inoculation with a group A streptococcus of a type different from that which the rabbit had previously received. As it was obviously impossible to induce repeated infections in rabbits' throats, or to observe them satisfactorily if they were so induced, it was planned to test the effect of using the animals' skin as the organ for successive inoculations, and to employ varying intervals, each of several months' duration, between inoculations. Occasionally the same streptococcal type was employed twice. The results of these experiments, carried out by Dr. George E. Murphy and myself over a period of two and a half years, have been recently recorded.<sup>56</sup>

Briefly summarized, the results were as follows: After sustaining several focal cutaneous infections, some rabbits sickened, but many of these recovered; a portion were sacrificed within 10 to 14 days following the last infection. In a few, however, a severe fatal illness developed after the last intracutaneous infection. These fell into two subgroups: in about half dying between six and 14 days following the last infection, streptococcal bacteremia was demonstrated at autopsy; in the other half, however, streptococci could not be cultured from the blood either before death or at autopsy. In the hearts of successively infected rabbits that sickened and succumbed, and of those sacrificed while sick, there occurred microscopically demonstrable lesions closely resembling those encountered in the hearts of patients dying with rheumatic fever. Focal collagen and intercellular ground substance alterations have occurred in vascular adventitia, valves, chordae tendineae, mural endocardium, epicardium and in myocardial interstitium unrelated to arteries or veins. Many swollen collagen fibers stained, either entirely or in patchy fashion, like fibrin with connective tissue technics. Interspersed in fields of swollen collagen and altered ground substance, there occurred nodular collections of large, irregularly shaped cells, often with abundant, finely granular, basophilic, indistinctly outlined cytoplasm. The variously shaped vesicular nuclei, single or multiple, had sharply defined membranes. Numerous cells with two to 12 centrally placed nuclei were seen in some hearts in mitral and aortic sulci and valve rings and in the endocardium. The submiliary granulomata found in these rabbit hearts closely resemble the coronal, reticular and mosaic types of Aschoff bodies. Mitral and aortic interstitial valvulitis was commonly found; and marked proliferation of mitral and aortic sulcus and valvular endocardial and subendocardial cells often formed palisades containing numerous multinucleated giant cells. There were coronary arterial lesions of the character seen in the hearts of rheumatic fever patients. Panarteritis of the so-called "allergic" or periarteritis nodosa type was, however, not present in these rabbits' hearts. Neither bacteria nor inclusion bodies were seen in these cardiac lesions. Noteworthy has been a distinct correlation between marked enlargement of

the adrenal cortex and the occurrence of myocardial granulomata in the rabbits dying, or sacrificed while sick, following the last of several cutaneous streptococcal infections. Several different sets of controls indicate that the experimental conditions apparently conducive to the induction of the lesions described were successive focal lesions caused by group A streptococci of different serological types.

From the results of these experiments it would seem unwise to assume, unreservedly, that rheumatic fever had been induced in these rabbits; but, on the other hand, to deny this possibility, in view of the data presented, would also be unjustified. Those investigators, notably Klinge and his collaborators<sup>57</sup> and Rich and his coworkers,<sup>58</sup> who have emphasized many points of similarity between the carditis seen in rabbits receiving one or more injections of foreign protein and that of rheumatic fever, have argued that these histopathological analogies indicate an "allergic factor" as being common to the two pathological states. It has been emphasized by Ehrlich et al.,<sup>59</sup> however, that there are enough histological diversities in the two conditions to indicate that they are not strictly comparable. Many years ago, in discussing Klinge's investigations, Aschoff<sup>60</sup> emphasized the hazard of attempting to establish the causation or essential nature of a disease by comparing one or two points of analogy with those of another disease. He insisted, that to prove a common causative factor in two such comparable conditions, a single common stimulus must be employed.

In investigating a possible etiological rôle of suspected microorganisms in a given disease and in planning a working hypothesis to test whether, and how, these microorganisms may induce this disease experimentally, it would seem quite important to duplicate, as closely as possible, the particular chain of circumstances under which these agents appear to induce the typical disease in nature. In the earlier part of this lecture are outlined the data obtained from applying current knowledge of group A streptococci and their antigenic components to the bacteriological and immunological studies of rheumatic fever patients; in the latter part is summarized how these data have been utilized in studying experimental streptococcal infections in rabbits. Eventually, by imposing on these animals infectious conditions approximately similar to those observed among rheumatic fever patients, there has been induced a histopathological picture in their hearts closely resembling that of human rheumatic carditis. The small proportion of infected rabbits showing this picture roughly approximated the relative frequency of rheumatic fever encountered among patients infected with group A streptococci.

On the basis of these investigations and of the hypothesis employed in planning them, there seems to be furnished additional support to the theory that group A streptococci are important factors in the pathogenesis of rheumatic fever; and the investigations also indicate how these microorganisms may act in giving rise to this disease.

## BIBLIOGRAPHY

1. PRIBRAM, A.: Der acute Gelenkrheumatismus, 1899, A. Hölder, Wien.
2. POYNTON, F. J., and PAINE, A.: Researches on rheumatism, 1913, J. & A. Churchill, London.
3. SCHOTTMÜLLER, H.: Die Artunterscheidung der für den Menschen pathogenen Streptokokken durch Blutagar, München. med. Wchnschr., 1903, 1, 849.
4. SWIFT, H. F.: The streptococci, Chapter 11, Bacterial and mycotic infections of man, edited by Dubos, 1948, J. B. Lippincott Co., Philadelphia.
5. LANCEFIELD, R. C.: Specific relationship of cell composition to biological activity of hemolytic streptococci, Harvey Lectures, 1940-1941, Series xxxvi, 251.
6. GRIFFITH, F.: The serological classification of *Streptococcus pyogenes*, Jr. Hyg., 1934, xxxiv, 542.
7. KUTTNER, A. G., and LENERT, T. F.: The occurrence of bacteriostatic properties in the blood of patients after recovery from streptococcal pharyngitis, Jr. Clin. Invest., 1944, xxiii, 151.
8. ROTHBARD, S.: Bacteriostatic effect of human sera on group A streptococci. I. Type-specific antibodies in sera of patients convalescent from group A streptococcal pharyngitis, Jr. Exper. Med., 1945, lxxxii, 93.
9. LANCEFIELD, R. C., and SWIFT, H. F.: Unpublished observations.
10. TODD, E. W.: Antigenic streptococcal hemolysin, Jr. Exper. Med., 1932, lv, 267.
11. TODD, E. W.: Antihaemolysin titres in haemolytic streptococcal infections and their significance in rheumatic fever, Brit. Jr. Exper. Path., 1932, xiii, 248.
12. TILLET, W. S., and GARNER, R. L.: The fibrinolytic activity of hemolytic streptococci, Jr. Exper. Med., 1933, lviii, 485.
13. CHRISTENSEN, L. R.: Streptococcal fibrinolysis: A proteolytic reaction due to a serum enzyme activated by streptococcal fibrinolysin, Jr. Gen. Physiol., 1945, xxviii, 363.
14. KAPLAN, M. H., in collaboration with the Commission on Acute Respiratory Diseases: Studies of streptococcal fibrinolysis. III. A quantitative method for the estimation of serum antifibrinolysin, Jr. Clin. Invest., 1946, xxv, 347.
15. MEYER, K.: The biological significance of hyaluronic acid and hyaluronidase, Physiol. Rev., 1947, xxvii, 335.
16. SEASTONE, C. V.: Virulence of group C hemolytic streptococci of animal origin, Jr. Exper. Med., 1939, lxx, 361.
17. HIRST, G. K.: The effect of a polysaccharide-splitting enzyme on streptococcal infection, Jr. Exper. Med., 1941, lxxiii, 493.
18. ROTHBARD, S.: Protective effect of hyaluronidase and type-specific anti-M serum on experimental group A streptococcus infections in mice, Jr. Exper. Med., 1948, lxxxviii, 325.
19. DURAN-REYNALS, F.: Tissue permeability and the spreading factors in infection, Bact. Rev., 1942, vi, 197.
20. CROWLEY, N.: Hyaluronidase production by haemolytic streptococci of human origin, Jr. Path. and Bact., 1944, lvi, 27.
21. PIKE, R. A.: Streptococcal hyaluronic acid and hyaluronidase. I. Hyaluronidase activity of noncapsulated group A streptococci, Jr. Infect. Dis., 1948, lxxxiii, 1.
22. PIKE, R. A.: Streptococcal hyaluronic acid and hyaluronidase. II. Production and subsequent destruction of hyaluronic acid by certain strains of group A streptococci, Jr. Infect. Dis., 1948, lxxxiii, 13.
23. QUINN, R. W.: The antihyaluronidase content of human blood serum, Jr. Immunol., 1949, lxii, 185.
24. HARRIS, T. N., and HARRIS, S.: Studies in the relation of the hemolytic streptococcus to rheumatic fever. V. Streptococcal anti-hyaluronidase (mucin-clot-prevention) titers in the sera of patients with rheumatic fever, streptococcal infection, and others, Am. Jr. Med. Sci., 1949, ccxvii, 174.

25. ELLIOTT, S. D.: A proteolytic enzyme produced by group A streptococci with special reference to its effect on the type-specific M antigen, *Jr. Exper. Med.*, 1945, lxxxi, 573.
26. McCARTY, M.: The occurrence of nucleases in culture filtrates of group A hemolytic streptococci, *Jr. Exper. Med.*, 1948, lxxxviii, 181.  
Personal communication about antibody formation by patients.
27. WATSON, R. F.: Personal communication.
28. HERBERT, D., and TODD, E. W.: The oxygen-stable haemolysin of group A haemolytic streptococci (streptolysin S), *Brit. Jr. Exper. Path.*, 1944, xxv, 242.
29. BERNHEIMER, A. W., and ROBBART, M.: The effect of nucleic acids and of carbohydrates on the formation of streptolysin, *Jr. Exper. Med.*, 1948, lxxxviii, 149.
30. COBURN, A. H.: The factor of infection in the rheumatic state, 1931, Williams and Wilkins Co., Baltimore.
31. SHELDON, W.: On acute rheumatism following tonsillitis, *Lancet*, 1931, i, 1337.
32. SCHLESINGER, B.: The relationship of throat infection to acute rheumatism in childhood, *Arch. Dis. Child.*, 1930, v, 411.
33. GRIFFITH, F.: Types of haemolytic streptococci in relation to scarlet fever, *Jr. Hyg.*, 1926, xxv, 385.
34. GLOVER, J. A., and GRIFFITH, F.: Acute tonsillitis and some of its sequels; epidemiological and bacteriological observations, *Brit. Med. Jr.*, 1931, ii, 521.
35. KUTTNER, A. G., and KRUMWIEDE, E.: Observations on the effect of streptococcal upper respiratory infections on rheumatic children—a three-year-old study, *Jr. Clin. Invest.*, 1941, xx, 273.
36. ANDERSON, H. C., KUNKEL, H. G., and McCARTY, M.: Quantitative antistreptokinase studies in patients infected with group A hemolytic streptococci: a comparison with serum antistreptolysin and gamma globulin levels with special reference to the occurrence of rheumatic fever, *Jr. Clin. Invest.*, 1948, xxvii, 425.
37. FRIOU, G. J., and WENNER, H. A.: On the occurrence in human serum of an inhibitory substance to hyaluronidase produced by a strain of hemolytic streptococcus, *Jr. Infect. Dis.*, 1947, lxxx, 185.
38. QUINN, R. W.: Antihyaluronidase studies of sera from patients with rheumatic fever, streptococcal infections, and miscellaneous non-streptococcal diseases, *Jr. Clin. Invest.*, 1948, xxvii, 471.
39. HARRIS, T. N., HARRIS, S., and NAGLE, R. L.: Studies in the relation of the hemolytic streptococcus to rheumatic fever. VI. Comparison of streptococcal antihyaluronidase with antibodies to other streptococcal antigens in the serum of patients with rheumatic fever and acute streptococcal infection: mucin clot prevention test, *Pediatrics*, 1949, iii, 482.
40. GUERRA, F.: Hyaluronidase inhibition by sodium salicylate in rheumatic fever, *Science*, 1946, ciii, 686.
41. HARRIS, T. N., and FRIEDMAN, S.: Studies in the relation of hemolytic streptococci to rheumatic fever. IV. Effect of streptococcal spreading factor in rheumatic patients and others, *Am. Jr. Dis. Child.*, 1949, lxxvii, 561.
42. TODD, E. W., COBURN, A. F., and HILL, A. B.: Antistreptolysin S titres in rheumatic fever, *Lancet*, 1939, ii, 1213.
43. ROTHBARD, S., WATSON, R. F., SWIFT, H. F., and WILSON, A. T.: Bacteriologic and immunologic studies on patients with hemolytic streptococcal infections as related to rheumatic fever, *Arch. Int. Med.*, 1948, lxxxii, 229.
44. SWIFT, H. F., and HODGE, B. E.: Type-specific anti-M precipitins in rheumatic and non-rheumatic patients with hemolytic streptococcal infections, *Proc. Soc. Exper. Biol. and Med.*, 1936, xxxiv, 849.
45. COBURN, A. F.: Observations on the mechanism of rheumatic fever, *Lancet*, 1936, ii, 1025.
46. WATSON, R. F., ROTHBARD, S., and SWIFT, H. F.: Type-specific protection and immunity following intranasal inoculation of monkeys with group A hemolytic streptococci, *Jr. Exper. Med.*, 1946, lxxxiv, 127.



47. ALLISON, V. D., and BROWN, W. A.: Reinfection as a cause of complications and relapses in scarlet fever wards, *Jr. Hyg.*, 1937, xxxvii, 153.
48. MASSELL, B. F., DOW, J. W., and JONES, T. D.: Orally administered penicillin in patients with rheumatic fever, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 1030.
49. POWERS, G. F., and BOISVERT, P. L.: Age as a factor in streptococcosis, *Jr. Pediat.*, 1944, xxv, 481.
50. ANDREWES, C. H., DERICK, C. L., and SWIFT, H. F.: The skin response of rabbits to non-hemolytic streptococci. I. Description of a secondary reaction occurring locally after intradermal inoculation, *Jr. Exper. Med.*, 1926, xliv, 35.
51. DERICK, C. L., and SWIFT, H. F.: Reactions of rabbits to non-hemolytic streptococci. I. General tuberculin-like hypersensitiveness, allergy, or hyperergy following the secondary reaction, *Jr. Exper. Med.*, 1929, xlix, 615.
52. SWIFT, H. F., and DERICK, C. L.: Reactions of rabbits to non-hemolytic streptococci. II. Skin reactions in intravenously immunized animals, *Jr. Exper. Med.*, 1929, xlix, 883.
53. BÖHMIG, R., and SWIFT, H. F.: Comparative histologic reactions in cutaneous lesions induced by streptococci in rabbits previously inoculated intracutaneously or intravenously, *Arch. Path.*, 1933, xv, 611.
54. BÖHMIG, R.: Über homologe und heterologe Testinfektionen mit Streptokokken in verschiedenen Stadien der Immunität, *Ztschr. f. Hyg. u. Infektionskrank.*, 1933, cxv, 406.
55. SWIFT, H. F., and HARTMAN, T. L.: Unpublished observations.
56. MURPHY, G. E., and SWIFT, H. F.: Induction of cardiac lesions, closely resembling those of rheumatic fever, in rabbits following repeated skin infections with group A streptococci, *Jr. Exper. Med.*, 1949, lxxxix, 687.
57. KLINGE, F.: Der Rheumatismus, pathologisch-anatomische und experimentelle-pathologische Tatsachen Auswerten für das Ärztliche Rheumatismus, *Ergb. allg. Path. u. path. Anat.*, 1933, xxvii, J. V. Bergmann, München.
58. RICH, A. R.: Hypersensitivity in disease, with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis, *The Harvey Lectures*, 1946-1947, Series xlii, 106.
59. EHRLICH, W. E., SEIFTER, J., and FORMAN, C.: Experimental serum disease: a pathogenic study, *Jr. Exper. Med.*, 1949, lxxxix, 23.
60. ASCHOFF, L.: Über den Begriff der allergischen Krankheiten, *Med. Klin.*, 1935, xxxi, 1.

# SODIUM SUCCINATE—AN ANALEPTIC FOR BARBITURATE POISONING IN MAN\*

By RICHARD H. BARRETT, M.D., M.Sc., *Hanover, New Hampshire*

THE barbiturates, next to carbon monoxide, are the most frequent source of poisoning, both suicidal and accidental.<sup>2</sup> This may well be attributable to the widespread use of the barbiturate drugs<sup>1</sup> as evidenced by the fact that in 1945, alone, over 290 tons of this one group of hypnotics were produced.

This paper reports an investigation of the effects of a new analeptic agent, sodium succinate, in the treatment of poisoning with barbituric acid compounds.

The present and generally accepted treatment of barbiturate poisoning<sup>3</sup> consists of one or all of the following procedures with, possibly, others: (a) Administration of oxygen, alone or in combination with carbon dioxide, to combat anoxia; (b) administration of intravenous fluids, to increase, supposedly, kidney filtration and thereby remove the barbiturate, at an increased rate; (c) gastric lavage, employed very early, in an attempt to remove the depressant drug, provided it were ingested; and (d) probably the most outstanding of all, the use of various convulsant drugs given intravenously. Picrotoxin, an outstanding example of the convulsants, first came into general usage in 1936. Since that time, it has been the drug most commonly used in the treatment of barbiturate poisoning.<sup>4</sup>

One may accept readily the use of oxygen and certain intravenous fluids as supportive therapy. However, gastric lavage should be used rarely, if ever, on a comatose patient with suspected barbiturate poisoning, because of the danger of inducing vomiting and consequent aspiration of stomach contents.

The use of convulsant drugs in the treatment of barbiturate poisoning while justified in critical situations is not without danger. In accidental and, especially, in suicidal barbiturate poisoning, exact dosage and type of barbiturate consumed is rarely known; therefore, a safe dosage of convulsant is difficult to determine. It has been stated that should a convulsion develop during the use of a convulsant drug, the convulsion may be controlled easily by giving more barbiturate.<sup>4</sup> This procedure could lead to disastrous results. Certain convulsants, given in subconvulsant doses, may prolong the later stages of recovery from the effects of hypnotics, and this secondary depression may be accompanied by pulmonary edema.<sup>5</sup> Hence there is possibility of underdosage, as well as overdosage.

\* Presented at New England Sectional Meeting of the American College of Physicians, January 28, 1947.

From the Hitchcock Clinic, Mary Hitchcock Memorial Hospital, Hanover, New Hampshire.

Unexplained coma, or deep narcosis, may be assumed mistakenly to be the result of barbiturates. Radical therapy with convulsant drugs in such an instance diminishes the patient's chance for recovery. Unfortunately, the "do-something" attitude is usually present when a possible suicide or accidental poisoning is concerned and accurate diagnostic procedures may be side-stepped. In most cases of supposed barbiturate poisoning, until diagnostic tests have been made, symptomatic treatment, especially the maintenance of an adequate airway, may be, not only the safest, but also the wisest treatment. When compared with the large number of so-called "barbiturate poisonings," death from the barbiturates, per se, is comparatively rare. Some of the deaths that do occur must be attributed to idiosyncrasies, because of the small dosage of drug consumed. Some deaths are undoubtedly the result of treatment. Many, possibly most, fatalities are due to serious complications in the respiratory tract.

If some drug were available that could be used safely in unproved as well as proved cases of so-called "barbiturate poisoning," it should have an important place in the armamentarium of most physicians. Sodium succinate is, apparently, so qualified.

The possibility of using sodium succinate as an antidote for barbiturate poisoning was suggested by Soskin and Taubenhaus in 1943.<sup>6</sup> Their suggestion was based primarily on animal (rat and dog) experimentation; however, they did report that in a case of combined barbiturate and picrotoxin poisoning in a human the intravenous use of sodium succinate "appeared to be of benefit." The patient recovered. They did not imply that this single case proved "anything," but they did state that it indicated the desirability for further investigation on human material.

Interest in their findings was shown by the appearance of subsequent reports on the effect of succinate in barbiturate poisoning in several controlled series with animals, and recently a preliminary<sup>7</sup> and a detailed report<sup>8</sup> on a controlled clinical series.

Review of the literature covering the use of sodium succinate in the treatment of experimental barbiturate poisoning in laboratory animals<sup>3</sup> leaves one in confusion regarding the existence of any analeptic quality in this agent.

#### MATERIAL

A 30 per cent aqueous solution of the hydrated salt of sodium succinate (disodium succinate hexahydrate)\* was used in the investigation to be reported. Sodium succinate is a salt of succinic acid, one of a group of four-carbon dicarboxylic acids. The actual mode and site of action of sodium succinate, as an analeptic, in barbiturate poisoning has not been determined. It is probable that this action is intimately concerned with tissue respiration and the rôles of succinoxidase and probably cytochrome oxidase. The pos-

\* This solution was supplied for the purpose of this investigation under the name "Soduxin" by Brewer and Company of Worcester, Massachusetts.

sibility of a reflex mechanism, based on the hypertonicity of the agent used, has been considered. A brief discussion relative to the possible mode of action of succinate has been presented elsewhere.<sup>3</sup>

Sodium succinate is a hexahydrated salt; therefore, the actual concentration of the solution used was about 18 per cent, rather than 30 per cent. This solution is stable at normal room temperatures (20° to 25° C.) but it becomes less effective or completely ineffective, as an analeptic, if allowed to remain at higher temperatures.

In an earlier report,<sup>3</sup> a series of 70 clinical cases that had received sodium succinate after Pentothal Sodium anesthesia ("controlled barbiturate poisoning") was compared, with a similar series that received only Pentothal. The results of that investigation demonstrated that sodium succinate when used, according to a simple procedure, was definitely effective in shortening the sleeping times of the cases in the experimental series. The results were often quite dramatic.

The purpose of the present investigation was to evaluate the effectiveness of sodium succinate used in man for the treatment of "uncontrolled" (that is, suicidal or accidental) barbiturate poisoning. The effect of the drug in 15 cases was studied. All subjects in this investigation had, or were diagnosed tentatively as having, "barbiturate poisoning"—produced accidentally or with suicidal intent. All were from rural areas. They were treated in a community hospital or in the home.

### METHOD

There was no specific preparation of the barbiturate poisoning cases previous to their initial treatment with sodium succinate. Manual or mechanical removal of any obstruction to the airway was a routine. When indicated, an artificial, pharyngeal or endotracheal, airway was introduced. (The endotracheal tube facilitates proper cleaning of the tracheo-bronchial tree.) The recumbent patient was placed usually in a slightly head-down position. Gastric lavage was *never* used.

Sodium succinate was given intravenously, immediately following the routine, preliminary procedures, just mentioned. The first 3 to 5 c.c. of succinate solution were injected rapidly—usually at the rate of 1 c.c. per second. The remainder of any indicated quantity was given more slowly. There is no fixed dose for sodium succinate; it should be given intermittently as indicated.<sup>3</sup>

Injection was delayed for 10 to 20 seconds after the initial dose. Typically, patients coughed once or twice during that brief pause. The cough was taken as a sign of adequate initial dose. If no cough were produced by the first dose, the dose was repeated. Unanesthetized human volunteers have described the subjective stimulus for the cough as being similar to that sensation which one experiences on taking a large drink of what he expects to be straight gingerale, but which proves to be straight whiskey!

Following the cough and a typical increase in depth of respiration, a crimson flush (the "succinate flush") appeared in the blush areas.

Intravenous injection of succinate was continued until definite analeptic responses were evident, such as groaning, voluntary movement of body, opening of eyes, etc. Occasionally, 30 to 45 grams (100 to 150 c.c.) of the agent were given within 15 to 20 minutes. Dosages employed in each of the 15 cases are indicated in table 1.

### DATA

This report is based on observations in 15 cases of "barbiturate poisoning" treated with sodium succinate. There were no deaths—from poisoning or therapy. In 14 of these 15 cases, the causative agents were, wholly or in part, barbiturate acid compounds. Coma in the remaining case was believed, originally, to be due to a barbiturate, but later the responsible factor proved to be of physical origin. This case has been reported previously<sup>3</sup> but it will be repeated here, for an obvious purpose.

The "poisoning" drug and the number of cases concerned in this series were divided as follows (table 1): barbital ("Veronal"), two cases (No. 1, 3); phenobarbital ("Luminal"), two cases (No. 6, 10); amytal and the so-called "short-acting"<sup>8</sup> barbiturates, sodium amytal, pentobarbital sodium ("Nembutal") and "Seconal," seven cases (No. 4, 5, 7, 9, 11, 12, 13); and three cases (No. 8, 14, 15) of idiosyncrasy to, or overdosage of, Pentothal Sodium. Two of the group had taken a combination of things. There were five males and 10 females. The poisonings occurred in a period of about two years (1945 and 1946). These 15 cases are not a true indication of the number of so-called "barbiturate poisoning" cases that were seen during that time, but they were cases for whom an analeptic agent seemed indicated.

Two of the males (aged 60 and 66) had been markedly depressed by relatively small doses of Pentothal Sodium; each received about 0.5 gram in a 2.5 per cent solution, given over a relatively long period. Their depression was due, possibly, to poor physical condition and age, either of which may be a factor in sensitivity to Pentothal Sodium, but from comparison with similar cases, it appeared to have been the result of idiosyncrasy.

Another male, aged 61, received 1.3 grams of Pentothal in 15 minutes. Obviously, this was a large dose, but apparently it was necessary for the patient and the type of surgical operation concerned.

One male (No. 1) had been hospitalized formerly in a psychiatric institution because of previous attempts at suicide.

The last male (No. 13) of this series was a pharmacist who had taken "Seconal" in repeated doses "for relief of pain."

Six of the 10 females had taken barbiturates with suicidal intent. One of the others (No. 10), although not an epileptic, had taken more than six grains (0.39 gram) of phenobarbital daily in the previous 10 years. She was hospitalized because of convulsions alternating with coma. Barbiturates had been denied the patient previous to admission. She was demonstrating withdrawal signs of chronic barbiturate poisoning.

One case (No. 6), a 64 year old woman, had fallen downstairs several days before admission. Her only complaint to her family physician, relative to her fall, had been

TABLE I  
Sodium Succinate—An Analeptic for Barbiturate Poisoning in Man

Identification	No.	Sex	Age	Type and Dosage of Barbiturate	Narcosis Time			Dosage of Sodium Succinate 3 gm./10 c.c.	Narcosis Time after Succinate Therapy	T.N.T.	Comments
					Outside Hospital	Inside Hospital	Total N.T.				
42438 P. II.	1	M	61	Barbital gr. 125 (8.3 grams)	5°	42°	47°	30 gm. (100 c.c.)	15' opened eyes 45' oriented—to status quo	47°45'	Known psychopath. Negativism and bed boards on awakening.
42903 C. T.	2	F	56	None (cerebrovascular accident)	10°	3°	13°	20 gm. (200 c.c. of 10%)	30'	14°	? of cerebrovascular accident before succinate therapy. Later proved by autopsy.
47840 L. R.	3	F	58	Barbital gr. 150 (10 gm.) Nembutal, 4.5 gr.	28+1°	1°	30°	30 gm. (100 c.c.)	5' cough 2°35' oriented	32-33°	Nembutal taken with one ounce of elixir of phenobarbital. Chin relaxed on admission.
41613 P. C.	4	F	23	Seconal, gr. 19.5 (1.3 gm.)	9-10°	15'	9-10°	42 gm. (140 c.c. 3°)	4° oriented	14°	Pupils exhibit reverse reaction to light, for first 30' of succinate therapy.
30088 A. H.	5	F	66	Nembutal, gr. 13.5 (0.9 gm.) Capritol (?)	2°30'	1°	3°30'	4.5 gm. (15 c.c.)	10' cough 15' turning 20' oriented	4°	(Amyotrophic lat. sclerosis)
42225 R. D.	6	F	64	Phenobarbital (repeated doses) Amt.?	3 days ?	1 day	4 days	4.5 gm. (15 c.c.)	24° oriented	5 days	Pt. had fallen down stairs. Phenobarb. given for relief of physical discomfort (pain). Memory loss after first or second dose.
42226 A. F.	7	F	45	Amytal (amount ?)	10°	7°	17°	6 gm. (20 c.c.)	10' cough 1°30' groan 3° opened eyes	17°3'	Told family she had taken "sleeping pills." They didn't believe her for 10 hours.
50427 A. H.	8	M	66	Pentothal (2.5%) (450 mg. in 15') for surg.	—	7°	7°	3 gm. (10 c.c.)	10' cough 5' tingling in face	7°5'	Normal B. P. 110/70. Before succinate 90/50. After 150/90; then in 5' to 110/70.
46560 M. S. O.	9	F	48	Sod. amytal, gr. 6 (0.4 gm.)	8°	1°	9°	3 gm. (10 c.c.)	20' cough 20' oriented	9°21'	Possible idiosyncrasy to drug or memory loss by pt. re ant. of amytal taken.
48752 P. N.	10	F	40	Phenobarbital, gr. 6.75 daily for 10 years	Semi-com.	Semi-com.	Semi-com.	3 gm. (10 c.c.)	1' (increased depth of respiration)	1°	Pt. exhibiting withdrawal symptoms of chronic barbitol poisoning.
45863 D. M.	11	F	3	Nembutal, gr. 4½ (0.3 gm.); Phenobarb.; nail polish remover.	2°45'	3°	5°45'	3 gm. (10 c.c.) Initial 15 gm. (50 c.c.) Total in 3°	2' cough 3° oriented	7-8°	Unknown amt. of phenobarb. taken. One ounce of nail polish remover (acetone).
598 A. C.	12	F	38	Nembutal, gr. 15 (1 gm.)	30'	Not in Hosp.	30'	6 gm. (20 c.c.)	15' cough 1' talking	31'	Not admitted to hospital.
47227 L. Y.	13	M	63	Seconal, gr. 27 (1.8 gm.) Divided doses.	10°	20'	10°20'	6 gm. (20 c.c.) Initial 21 gm. (70 c.c.) Total	10' cough 2° oriented	12°30'	Pharmacist. Second taken for relief of pain (self treatment). Could be roused but was disoriented. Memory loss.
30487	14	M	61	Pentothal (2.5%) 55 c.c. (1375 mg.) given in 15' for surgery.	—	20'	20'	2.8 gm. (9 c.c.) Initial 6 gm. (20 c.c.) Total	5' groaning 30' moving head and body	50'	Pt. in laryngospasm when succinate given. This stopped in 20'.
36718	15	M	60	Pentothal (2.5%) (550 mg.) For surgery.	—	25'	25'	6 gm. (20 c.c.)	1' cough 5' eyes open	30'	Pupils pin point before succinate, dilated after 3 c.c.

° equals hour. ' equals minute. '' equals second.

"sleeplessness because of little aches and pains." Phenobarbital had been prescribed for this complaint. The initial dose of one-half grain (0.03 gram) was "to be repeated once, if necessary." After recovery, this patient remembered, vaguely, that she had taken "one or two more tablets." However, when her family discovered that she could not be aroused, they also noted the empty medicine box. From the *patient's* standpoint, this was a case of accidental poisoning.

A three-year old girl (No. 11) had taken a combination of "Luminal and Nembutal-C tablets" with an ounce of fingernail polish remover as a "chaser" before admission to the hospital.

The remaining female of the series was a 56-year old housewife who was brought to the hospital because of probable barbiturate poisoning. She had been found asleep in her bed late in the morning. When her son could not arouse her, he became alarmed and called their family physician. On admission to the hospital, she was described as having been "found in a comatose state and with absent reflexes." One physician made an admitting diagnosis of "cerebro-vascular accident and cardiac failure with passive congestion." Another physician wrote: "probable barbiturate poisoning." Shortly after these temporary diagnoses were made, a relative of the patient appeared with a box containing, what he described as "sleeping pills." The partially filled box had been found in the patient's home under her bed. Admitting diagnoses of the two physicians were not changed. An anesthesia service consultation was requested. These physicians were aware of this service's interest in the use of succinate on this type of case, that is, a case in coma of questionable etiology.

Two hours after admission of the patient, physical findings were unchanged; notably, knee jerks and ankle jerks were still absent, and it was necessary to hold the patient's jaw in order to maintain an adequate airway. At this time, a solution containing 10 per cent sodium succinate and 5 per cent dextrose was started by intravenous clysis at a rate of 20 drops (1.6 c.c.) per minute. Twenty minutes later, 30 c.c. of this solution were injected, as a single dose, in one minute. In the next minute the patient opened her eyes, responded to her name by groaning, and moved her left arm and leg in an attempt to turn. Knee jerk on the left was normal, but absent on the right. There was a right-sided flaccid hemiplegia.

Dilute (10 per cent) succinate solution was given at the rate of about 75 drops per minute, for the next 30 minutes, or until a total of 200 c.c. had been taken.

The patient remained in a semi-conscious state during the next three hours and could be aroused easily throughout the remainder of the night (about six hours).

She died two days later. The findings at autopsy were "arteriosclerosis of cerebral vessels" and "recent infarct of left cerebrum." That this patient *was*, at the time of treatment with succinate, suffering from cerebral anoxia is probable. That sodium succinate *did* relieve, in some way, at least *temporarily* and *in part*, the anoxic state is suggested by events. That the case was one of barbiturate poisoning is improbable. And—although the patient was not cured with the agent used—certainly, the use of any convulsant drug was contraindicated in this case and would be in others of similar type. The "sleeping pills" contained, principally, an ephedrine-like compound.

Three cases, typical of the series investigated, will be presented. The first is that of a widow, aged 58, who was admitted to the hospital after a total narcosis time (T.N.T.), elsewhere, of about 30 hours. During that time, breathing was reported as having been "adequate," but she had been flaccid and could not be aroused.

Her blood pressure on admission was 100 mm. Hg systolic and 60 mm. diastolic. Radial pulse rate was 80 per minute and respiratory rate was 16 per minute. Breathing was very shallow. It was necessary to support her lower jaw to provide an adequate airway. Removal of a moderate amount of tenacious mucus from the oropharynx improved breathing.

While the patient was being examined, 5 c.c. of 30 per cent sodium succinate were given rapidly, by vein. After five seconds, the patient coughed and moved her right leg. Systolic blood pressure increased by 10 mm.

Three minutes after the initial injection, an additional 10 c.c. of succinate solution were given rapidly. The immediate effect was a marked increase in depth of respiration without any remarkable change in rate. The blood pressure was then 120/80.

During the first 10 minutes of therapy, the patient received 50 c.c. of succinate solution. (This was equivalent to 15 grams of hydrated sodium succinate or 9 grams of the anhydrous form.) Following this dose, the eyelid reflex was present and she was moving her legs. A crimson flush was present in the blush areas.

An intravenous clysis of 10 per cent succinate and 5 per cent glucose was started at a slow drip-rate. Fifteen minutes later, the patient was slightly cyanotic. A large amount of thick, tenacious mucus was removed from the pharynx; the infusion rate was increased; and, for five minutes, 100 per cent oxygen was given by face mask.

Two hours and 35 minutes after the start of succinate therapy, the patient was well oriented and talking coherently. She stated that she had taken "4½ grains (0.3 gram) of Nembutal, and one ounce of elixir of phenobarbital." This, certainly, was *not an excessive dose*, especially considering the fact that, according to her home physician, she was not abnormally susceptible to the usual effects of these drugs; however, two hours later, she "remembered" also 30 five-grain barbitol tablets (150 grains or 10 grams) that she had taken with the other hypnotics.

This woman received 100 c.c. of 30 per cent sodium succinate (30 grams of the hydrous salt) in two hours and 35 minutes.

A three-year-old girl, who, at the time of admission, was comatose, moderately flaccid, and unresponsive to normally painful stimuli, with acetone-like breath and rapid respirations, had signs of pulmonary edema on the right. The child had no history of diabetes and, obviously, was not undernourished.

Total narcosis time before admission was indefinite, but it was not more than two and three-quarters hours.

The history of this case previous to admission was essentially as follows: The patient's five-month-old brother had been, supposedly, having his mid-morning nap. Their mother had been busy with housework until she went into the baby's room to get something. There, she found the patient "sound asleep on the floor," and the baby "wide awake in his crib." Several different types of tablets and pills were scattered on the floor; also, a new, four-ounce bottle of nail polish remover was open and only three-fourths full. The family physician was called and the patient was brought to the hospital.

Three hours after admission there had been no appreciable change in the patient's general condition. The respiratory rate remained rapid and shallow, and the child continued to be comatose and unresponsive.

At this time, 10 c.c. of sodium succinate (30 per cent) were given, in two minutes. During the initial course of the injection, the patient demonstrated the typical cough, following which she swallowed several times. A "succinate flush" appeared on her face and arms. Respirations became deeper.

Two and one-half hours later, an intravenous clysis of 10 per cent succinate and 5 per cent glucose in water was started.

Within the next half-hour, the succinate flush covered practically her entire body. The patient reacted to painful stimuli and opened her eyes, when requested to do so.

Although ataxic, she was well oriented in the following hour and asked for "a good lunch and a big glass of milk." She got both and consumed both. This was less



than five hours after admission, or a possible total narcosis time of seven to eight hours.

While the child was eating this lunch, specimens of drugs, known to have been present in the mother's bedroom, were spread on a tray by the patient's bed. This was placed in a conspicuous position before her, as she told how "bad Baby Brother" (all five months of him!) had "jumped out of his crib" and "spread medicine all 'round.'" She continued by saying that he had eaten "three of these" (Nembutal-C,  $4\frac{1}{2}$  grain or 0.3 gram, total) and "lots of those" (phenobarbital, unknown amount). She concluded her revelations with: "and then he took a big drink of the new nail polish!" Actually, it was nail polish remover, rather than polish, and "Baby Brother" was, in no way, involved. Chemical analysis confirmed the belief that this particular nail polish remover was principally acetone.

This young patient received 50 c.c. of sodium succinate (equivalent to 18 grams of the hydrous salt) in three hours. The initial dose was 3 grams, or 10 c.c. of the stock solution, given in two minutes. The remainder was given as a 10 per cent solution combined with 5 per cent glucose.

The remaining case to be described was that of a male, aged 64, who had been diagnosed previously as being psychopathic. It was known that he had taken 125 grains (8.1 grams) of barbital. For the depression that followed, he had been given 16 c.c. of 0.3 per cent picrotoxin, by his local physician, 30 minutes before hospital admission. This had produced a convulsion. However, at the time of admission he was again in deep narcosis.

This patient was given common supportive treatment during the first 24 hours in the hospital. There was no improvement in his general condition. In the twenty-fifth hour, he was given 100 c.c. of sodium succinate solution (equivalent to 30 grams of sodium succinate). Within 15 minutes, he responded and, within an hour, he was as well oriented, allegedly, as he had been before taking barbital. There were no convulsions, and he did not go to sleep again for several hours. In fact, it was necessary to put side boards on his bed, because he insisted on getting out and wandering around the ward.

## DISCUSSION

In order that the effects of therapy shall not be more harmful than the condition being treated, there is an ever-present need for marked carefulness in the treatment of barbiturate poisoning and the need is even greater in the treatment of *supposed or assumed* "barbiturate poisoning." From this and previous investigations, by the author, on man, it appears that sodium succinate may be used safely in any stage of narcosis or in the quite awake individual.<sup>7</sup> It has been demonstrated many times that the analeptic effect of succinate on man is directly related to the depth of narcosis, that is, the greater the need, the more marked is the effect—or, the less the need, the less will be the effect.

In relation to this finding, it is interesting to note an observation made by Banga, on tissue cultures, as stated by Elliott: "Banga showed that it was not easy to remove all the four-carbon (dicarboxylic) acids from tissue. It is, therefore, possible that when added four-carbon dicarboxylic acids have little effect on the respiration of tissues, these substances may already be present in the tissues in such amounts that their concentration is not a limiting factor of the respiration rate."<sup>10</sup>

In several hundred administrations of sodium succinate to man, under various conditions and for various indications, there have never been visible convulsions nor production of excitement, beyond the *status quo* of the subjects concerned.

It has been stated that "patients with barbiturate poisoning fall into four groups, two of which recover and the remaining two do not. The first is the group of patients who recover without any treatment. All they require is general nursing. The second is the group of patients who die regardless of how intensive and expert the treatment is. They have simply taken so large a dose that no antidote or method of treatment can save them. The third group embraces those patients who recover only because of expert management; without the most effective measures most frequently applied they would succumb. The fourth embraces those patients who die because of the treatment."<sup>2</sup> Sodium succinate can be a factor in eliminating the last group and, probably, the second.

It may be helpful to know the amount of barbiturate a patient has taken, but this information is frequently inaccurate. It is, however, well to remember that adults are almost certain to recover, without specific treatment, from oral doses of the order of 1 or 2 grams of any of the commonly used barbiturates. The fatal dose is sometimes stated as being, in general, 15 to 30 times the therapeutic dose. It has been said that the dose of barbital which is nearly always fatal is about 10 grams, and that of phenobarbital, from 6 to 8 grams.<sup>9</sup> However, there are so many factors that may contribute to the depressing effect of the barbiturates, such as physical and mental fatigue, a very recent hot bath, analgesic drugs, etc., that discussions concerning any fixed, or even nearly fixed, so-called "fatal dose" have little, if any, value. Every case of barbiturate poisoning should be treated as an entity—regardless of drug taken, or supposedly taken. The greatest foe in the treatment of barbiturate poisoning is anoxia. The greatest foe in recovery from barbiturate poisoning may be the type of treatment employed.

A few years ago, before the use of succinate, a 17-year-old girl, who had taken an indefinite amount of phenobarbital, was admitted to our hospital. The quantity of drug concerned was estimated, by the referring physician, to be between 150 and 200 grains (10 to 13 grams). At the hospital, it was estimated that she would sleep for a week. She did.

During that entire week her position was changed every half hour, day and night, side to side, foot of bed elevated, then head of bed elevated. Some of the convulsant drugs were used, but only in relatively small doses. Supportive therapy was the main course of treatment. The maintenance of fluid, electrolyte and protein balances became a complicated problem. During the last four days of the week, a constant vigil was necessary. In order to maintain an adequate airway, it was necessary to bronchoscope the patient two or three times to remove thick, tenacious mucus from the tracheo-bronchial tree. Recovery was finally complete, and there were no apparent mental changes. However, it was a very exhausting ordeal, especially from the nursing standpoint. Without conscientious nursing care, recovery for this case would have been impossible. It is for cases of this type, especially, that succinate is indicated.

There are many cases of *so-called* "barbiturate poisoning" that require no specific treatment beyond adequate supportive care. It is well known that many patients, in certain depressive states, receive considerable benefit from prolonged sleep of 24 to 48 hours, or, possibly, longer. It is conceivable that some suicide patients may actually benefit by their self-poisoning with barbiturates *if* they are adequately protected against anoxia; however, the possibility cannot be relied upon.

### SUMMARY

The frequency of over-indulgence, by the general public, in the misuse of the barbituric acid compounds, that is, self-treatment—to the extent of addiction and attempted self-destruction—has been reiterated.

Generally accepted, supportive treatment of barbiturate poisoning has been reviewed. The difficulty involved in making a diagnosis of true "barbiturate poisoning" has been restated. The fact that making this diagnosis is often a time-consuming procedure has been emphasized.

A method for the use of sodium succinate in the treatment of comatose patients, having, or suspected of having, barbiturate poisoning, has been presented.

Fourteen cases of true barbiturate poisoning, that were treated with sodium succinate for the purpose of investigating its analeptic effect, have been reported. Three of these were presented in detail. There were no deaths in the series.

One case of suspected barbiturate poisoning, that later proved to be a case of cerebro-vascular accident, in coma, was presented. This case was reported for the purpose of indicating the possibility of harmful effects that may result from the use of convulsant drugs, in the treatment of a patient in coma of unknown etiology.

The author has had no untoward effects from the use of sodium succinate in man. Pulmonary edema has been reported in small animals, following rapid injection of this agent. It has not been observed in man, although large quantities have been injected, as rapidly as possible, through a 20-gauge needle.

The importance of treating each case of barbiturate poisoning as an entity has been stated.

### CONCLUSION

Sodium succinate is indicated for the treatment of "suspected" or "probable," as well as actual, barbiturate poisoning in man. This indication for succinate is based on the following: (1) its analeptic effect without, apparently, the possibility of producing convulsions, (2) its non-toxicity, and (3) its demonstrated property of aiding in the reestablishment of the status quo in the poisoned patient.

## BIBLIOGRAPHY

1. Federal officials puzzled by large United States consumption of sleeping pills, *Jr. Am. Med. Assoc.*, 1946, cxxxiii, 405.
2. Departments of Pharmacology and Medicine, Cornell University Medical College and the New York Hospital, Conferences. Conferences on Therapy; Treatment of Barbiturate Poisoning, *Am. Jr. Med.*, 1946, i, 93-103.
3. BARRETT, R. H.: The analeptic effect of sodium succinate on barbiturate depression in man, *Anesthesia and Analgesia*, 1947, xxvi, 74-81, 105-113.
4. DARCEY, J. F.: The picrotoxin treatment of barbiturate poisoning, *Jr. Nerv. and Ment. Dis.*, 1944, xcix, 367-375.
5. BARLOW, O. W.: The relative efficiency of a series of analeptics as antidotes to sublethal and lethal dosages of pentobarbital, chloral hydrate, and tribromethanol ("Avertin"), *Jr. Pharmacol. and Exper. Therap.*, 1935, lv, 1-22.
6. SOSKIN, S., and TAUBENHAUS, M.: Sodium succinate as an analeptic for barbiturate poisoning and in the control of the duration of barbiturate anesthesia, *Jr. Pharmacol. and Exper. Therap.*, 1943, lxxviii, 49-55.
7. CAMPBELL, C. J., MAES, J. P., and BARRETT, R. H.: Sodium succinate as an analeptic in man, *Fed. Proc.*, 1946, v, 15.
8. FITCH, R. H., and TATUM, A. L.: Duration of action of barbituric acid hypnotics as a basis of classification, *Jr. Pharmacol. and Exper. Therap.*, 1932, xlv, 325-335.
9. RICHARDS, RICHARD KOHN: The therapy of barbiturate poisoning, *In: FANTUS, BERNARD: The therapy of the Cook County Hospital*, *Jr. Am. Med. Assoc.*, 1940, cxv, 527-529.
10. ELLIOTT, K. A. C.: The possible rôle of intermediary metabolites as hydrogen carriers. *In: A symposium on respiratory enzymes*, 1942, The University of Wisconsin Press, Madison, pp. 33-35.

## LOWER NEPHRON SYNDROME \*

By G. E. BURCH, M.D., and C. T. RAY, M.D., *New Orleans, Louisiana*

THE relatively high frequency with which the lower nephron syndrome, a highly fatal disease state, is observed clinically makes imperative a thorough acquaintance with the clinical picture. The syndrome is particularly common during wartime, when man receives bodily injury.<sup>15, 16, 61, 74</sup> It may be produced by transfusion reactions<sup>3, 24, 28, 31, 45</sup>; crushing injury,<sup>16, 30, 33, 47, 61, 83</sup> burns,<sup>38, 48, 63, 82</sup> heat stroke,<sup>68</sup> blackwater fever,<sup>41, 66, 105, 108</sup> toxemia of pregnancy, uteroplacental damage,<sup>109</sup> certain types of intoxications,<sup>27, 34, 36, 87, 101</sup> such as sulfonamide reactions,<sup>42, 43, 62, 94</sup> and other conditions.<sup>46, 57, 65, 70, 84, 110</sup> The high case fatality rate accentuates the need for a thorough knowledge of the disease, so that it may be managed properly and preventive measures may be instituted to reduce its incidence. It is the purpose of this presentation to review briefly the problem of the lower nephron syndrome, including the clinical picture, phases of its mechanism, prevention, and management.

A historical discussion of the lower nephron syndrome would have no particular value here. It is of interest, however, to note that the first papers on this subject were published in the German literature following the first World War.<sup>44, 52, 74, 79, 90</sup> Nevertheless, relatively little attention was given to the syndrome, despite the fact that a large number of such patients was encountered during battle. Probably the most interesting and important early paper was that published by Minami in 1923.<sup>74</sup> He described the clinical picture, indicated the nature of the damage, its relationship to crushing injuries, and also comprehensively presented the pathologic manifestations. Other papers include those of Ganter,<sup>44</sup> Landsberg and Gnoinski,<sup>58</sup> and Rosenak and Siwon,<sup>90</sup> which suggested the possible value of peritoneal lavage in the management of temporary acute renal damage.

Except for the reports on blackwater fever, transfusion reactions, mercurial, arsenic, and uranium poisoning, and toxemias of pregnancy, relatively little was published about the lower nephron syndrome before World War II. During the recent bombing of London, however, many English civilians received crushing injuries which presented a rather characteristic clinical picture. As a result of a study of these patients, Bywaters and his associates described the picture of the lower nephron syndrome again.<sup>15-22</sup> Various designations were employed: "crushing injury," "ischemic muscle necrosis with renal injury," "crush syndrome," "traumatic anuria," and "compression syndrome." A series of excellent papers by Bywaters and his group followed in rapid succession.

\* Received for publication March 28, 1949.

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans.

As Bywaters<sup>15</sup> pointed out, the disease is really not new. Similar cases had been encountered at least as early as 1909 by Colmers,<sup>23</sup> though they were not recognized. In 1946 Lucké<sup>61</sup> reported an excellent study of observations made on 538 fatal cases of "lower nephron nephrosis," as he called it.

Increased interest in and knowledge of the lower nephron syndrome and some of the acute anurias has resulted in more frequent use of the artificial kidney<sup>55, 56</sup> and other methods for the removal of toxic elements circulating in the blood of the anuric patient. Numerous papers have been published on the subject within the last few years and many more are sure to follow, especially since the possible clinical value of such procedures has been definitely realized.

### THE CLINICAL PICTURE

Before the more fundamental aspects of the lower nephron syndrome are discussed, it is advisable to review the clinical picture.<sup>16, 17, 61</sup> As stated previously, the *causative* agent varies widely. The patient suffering from a crushing injury which produces lower nephron nephrosis presents a history of having been pinned by heavy beams or pieces of masonry in such a manner that a considerable amount of tissue has been crushed. He has usually remained under the crushing force for several hours. As a rule, he appears to be in good condition soon after release except for wounds and local injuries, such as fractures and contusions. However, in a few hours he begins to show evidences of edema and slight oozing and hemorrhage into the injured tissues and from the wounds. He then passes quickly into the *first phase of shock*, which is considered by many to be due to loss of plasma through damaged capillary walls into the tissue spaces of the injured areas. These areas become extremely swollen, and the skin becomes shiny. Evidences of necrosis with bleb formation may appear. Loss of fluid into the tissue spaces results in hemoconcentration, evidenced by an increase in hemoglobin, hematocrit and erythrocyte count. During this phase of shock the skin tends to be pale, cold and moist, although the blood pressure generally remains essentially normal, apparently because of compensatory vasoconstriction. Occasionally when this vasoconstriction is not maintained, there follows a rapid drop in blood pressure, with the development of the *second phase of shock*. If plasma or fluids are administered at this time, the blood pressure will return to normal. With inadequate therapy shock may become irreversible.

The patient tends to show evidences of *anxiety*. The first or second samples of *urine* passed following the injury are noted to be bloody and to contain pigment suggestive of hemoglobin or altered hemoglobin. The urine also contains albumin, creatine, granular casts and pigment granules, which sometimes resemble intact erythrocytes. It is usually highly acid, with a pH of 4.6 to 6.0. The urine volume remains low and may even approach anuria. Oliguria continues despite fluid intake or any form of therapy. The specific gravity tends to become fixed at 1.010, correction having been made for the protein content.

In the meantime, the damaged tissue, as for example, the limbs or trunk, becomes so swollen, hard and tense that digital indentations cannot be readily made. This swelling usually progresses for the first four or five days. Petechial hemorrhages, erythematous wheals, and large blisters are usually noted at points of pressure over the injured structures and extend to adjacent areas. There may be patchy anesthesia of the involved area, probably related to damage of terminal nerve fibers. Paralysis of varying severity and extent generally develops. Arterial pulsations in the peripheral parts may be absent and the part may be cold and pale. Gangrene may occur.

The patient becomes apathetic, with alternating phases of anxiety and extreme apprehension. He is usually aware of the severity of his disease. About this time vomiting may be prominent; this is an important aspect of the manifestations because of its relationship to dehydration, malnutrition and disturbances in electrolyte balance. *Blood pressure usually rises gradually above the previous or normal level.*

Changes in chemical composition of the blood become evident at this stage. There is an accumulation of urea, potassium and phosphate in the blood; the carbon dioxide combining power progressively falls; and occasionally the blood chloride tends to decline in concentration, probably because of inability of the tubules to reabsorb chloride. The patient often experiences pain in the renal region, which is thought to be due to swelling of the kidneys with stretching of the capsule. The renal pain has been responsible for abdominal operations, performed erroneously in search of an acute abdominal operative state.

The end of the first week is usually the critical period. If the patient recovers, there is sudden diuresis, following which urinary output gradually rises to extremely high levels. Blood urea level falls, urea clearance improves, and tubular function shows evidences of returning to normal. During the recovery period, granular epithelial casts may be noted, replacing the pigment casts and erythrocyte casts present during the early phases of the disease. As a result of the pressure necrosis produced by crushing, damaged areas of skin, muscle and other tissues begin to slough. Severe infection may develop. With recovery, local fibrosis may become extensive and produce disturbances resembling Volkmann's ischemic contractures.

In some of the more severely injured patients cardiac irregularities may be noted at the critical period, and extreme electrocardiographic changes, particularly evident in the S-T segment and the T waves, begin to appear. The latter resemble changes described for potassium poisoning or those produced experimentally by intravenous administration of potassium. *Though the potassium level may be greatly increased during this period,* it is not yet known whether the levels attained in the lower nephron syndrome are sufficient to explain the electrocardiographic manifestations. Furthermore, potassium metabolism and the physiologic interrelationship of intra- and extracellular potassium are not well understood. It is well

known that damage to cells results in an escape of potassium into intercellular spaces.

If diuresis continues and if renal function progressively improves, the patient will make an apparently uneventful recovery. However, should diuresis fail to develop, there will ensue a continuous downward course, characterized by increasingly severe uremia with extreme mental disturbances, often terminating in coma. The patient often calls out with alarm, becomes pale, sweats profusely and the alae nasi become dilated. Death usually occurs suddenly, sometimes even within one or two minutes. He may recover from these episodes, only to be seized by another an hour or so later—one of them terminating fatally.

The general clinical pattern varies little with the responsible etiologic factors. The chief difference is in that phase of the patient's course concerned directly with the etiologic factors producing the entity. For example, in lower nephron nephrosis eventuating from a transfusion reaction there will be a history of administration of incompatible blood, followed by a severe chill and fever and then oliguria, hematuria, pigment and erythrocyte casts, and uremia, usually with ensuing death. Renal function decreases until the specific gravity is fixed at 1.010, and azotemia with retention of other toxic materials develops. In a patient who suffers a transfusion reaction, particularly postoperatively or as a result of treatment for an accident, various degrees of shock are liable to occur. *Shock* and *vomiting* are two of the associated manifestations which tend to precipitate or aggravate the oliguric state.<sup>10, 61</sup> It is interesting to note that in those patients who sustain such damage without the development of these two symptoms, the severity of the clinical state is not great.

When the lower nephron syndrome is produced by a reaction to sulfonamides, the patient has usually received the drug in the presence of an impaired cardiovascular system, such as congestive heart failure, or impaired renal function, with inadequate urinary output and often in the presence of acid urine.<sup>14, 107</sup> Hematuria occurs, associated with sulfonamide crystals in the urine and sometimes with pain over the renal regions. These patients, as a rule, do not manifest a shock-like state, although occasionally shock or peripheral circulatory collapse may occur, partially as a result of the reaction to the drug and partially as a result of the disease for which the drug was employed. The clinical course and general manifestations are essentially those described previously for the crush syndrome.

The clinical picture of the lower nephron syndrome also resembles that of the uteroplacental syndrome,<sup>109</sup> as encountered in postpartal sepsis or in criminal abortion with infection of the uterus. There is a difference in the clinical pattern due to the infection, but as far as the renal portion of the picture is concerned, it is essentially identical.

In summary, the clinical picture produced by the various disease states is modified in part by the etiologic factors concerned with the production of that



particular syndrome.<sup>16, 17, 61</sup> It is not possible to discuss each of the factors which might be responsible for the syndrome, but they are summarized briefly in the accompanying table (table 1) and references to them have been included. It is advisable to discuss briefly certain clinical manifestations frequently encountered in the lower nephron syndrome.

TABLE I

Etiologic Factors in 538 Fatal Cases Having the Characteristic Renal Lesions of  
Lower Nephron Nephrosis

(Under most of the groups listed are given the number of cases which received transfusions of blood, sulfonamides, or both, as therapeutic measures)

Battle Wounds (Gunshot, mine explosion, blast injury, severance of large blood vessel, etc.)	221
Crushing Injuries	46
Abdominal Operations (Carcinoma of colon, stomach, pancreas, etc. ruptured ulcer of duodenum or stomach; ruptured appendix, etc.)	36
Burns	48
Blood Transfusion Reaction (In cases of trauma, poisoning, infections, etc.)	45
Sulfonamide Intoxication (In cases of meningitis, pneumonia, other nontraumatic infections, infections associated with trauma, etc.)	47
Heat Stroke	19
Malaria ( <i>Falciparum</i> ); Blackwater Fever	14
Poisons (Arsenicals, carbon tetrachloride, alkali, carbon monoxide, alcohol (adulterated), isopropyl alcohol, phenol, photodeveloper, mussel, mushroom)	20
Hemolytic Anemia (Etiology undetermined)	4
Miscellaneous (Uteroplacental damage, eclampsia, acute pancreatitis, "shock" from various causes, etc.)	38
From Lucké, Balduin: Lower nephron nephrosis, Military Surgeon, 1946, xcix, 372.	

(1) *Hypertension*. As stated previously, the blood pressure may decline, although generally it is maintained. Even if it falls to shock level, it rapidly returns to normal. In most patients observed, the fall has occurred on the first day, with restoration to normal on the second day of the disease, then a rise to 150 mm. Hg systolic and 90 mm. diastolic or slightly more on the third day. Thereafter this level is maintained or is even increased. The mechanisms for the changes in blood pressure are not known but apparently they are concerned with the usual factors associated with shock and renal dysfunction.

(2) *Edema*. There is usually a moderate amount of generalized edema. It is attributable to therapeutic procedures, such as parenteral administration of large amounts of fluids—an attempt on the part of the physician to force diuresis or to dilute the retained toxins. The edema in the local area injured by crushing or trauma is usually prominent, whereas that in the extremities and bases of the lungs is slight to moderate. Edema of the face is relatively uncommon except for slight puffiness; extreme facial edema is noted only in the more severely ill patients.

(3) *Uremia*. Uremia develops to some extent in all patients but is more severe in fatal cases. It is caused by the renal failure and is not due to other causes. However, such factors as repeated vomiting and disturbances in nutrition may contribute to the rate of production of azotemia and accumulation of toxic agents. Uremia begins within the first 24 to 48

hours, depending upon the rate of development of oliguria. However, the typical manifestations do not usually appear until the last two or three days of life. Vomiting and mental disturbances, such as irrationality, drowsiness and finally coma, are commonly associated symptoms. Convulsions are rare, as in any type of true uremia.

(4) *Fatality Rate.* The fatality rate is extremely high. Once the cardinal signs of oliguria, excretion of heme pigment, azotemia and hypertension develop, it reaches about 90 per cent. The course of the disease is relatively brief, and in fatal blood transfusion reactions the survival period is usually three to 10 days. In the crush syndrome death usually occurs by the end of the first week; most patients surviving eight to nine days recover. In one series<sup>61</sup> 74 per cent of the patients died within the first 48 hours. About 8 per cent of the patients who died have been reported to survive more than 12 days. It is not known whether death is due entirely to renal damage or in part to the precipitating cause itself, but it is quite likely that there are a number of contributing factors.

#### PATHOLOGY

The organic changes, other than those which occur at the primary site of injury by the etiologic agent, such as local tissue damage in the case of the crush syndrome or injury to the gastrointestinal tract in the case of mercurial poisoning, are largely confined to the kidneys.

*Gross Appearance of the Kidneys.* There are no pathognomonic gross manifestations of the lower nephron syndrome. The essential gross and microscopic manifestations are as follows<sup>8, 15-17, 30, 61, 74, 77</sup>: The kidneys are usually swollen and increased in weight, in some instances two or more times the normal weight. There has been no definite correlation between the size of the kidneys and the duration of the disease, although a certain amount of time is required for the swelling to develop. There is some suggestion that the increase in size of the kidneys after trauma or burns tends to be greater than that following nontraumatic conditions, such as transfusion reactions. Typically the kidney is somewhat soft, the capsule strips easily, the outer surface is pale, smooth and glistening, and a clear or slightly bloody fluid oozes from the cut surface. The cortex is widened and tends to bulge perceptibly. It is moist, pale and in sharp contrast to the dusky, somewhat cyanotic-appearing medulla. The striations are often greatly accentuated. A whitish stripe has been described in the inner aspect of the cortex.

*Microscopic Findings.* The histologic descriptions, including those of Bywaters and his group,<sup>15-17</sup> Minami,<sup>74</sup> Lucké<sup>61</sup> and Mallory,<sup>69</sup> have been summarized into four essentially distinct categories by Lucké<sup>61</sup>:

(1) There is degeneration and necrosis which involves somewhat selectively the lower part of the nephrons, that is, the thick portions of the loops of Henle and the distal convoluted tubules.

(2) Edema and inflammatory reactions develop in the interstitial spaces around the damaged and disintegrating tubules. These reactions are usually found where the tubular degeneration is most severe. Occasionally thrombosis of and severe damage to adjacent veins are seen. This interesting lesion is diagnostic.

(3) The heme casts of the lower portions of the tubules, including the collecting tubules, are characteristic.

(4) There are relatively slight or no histologic changes in the upper parts of the nephrons, that is, the glomeruli, proximal tubules and intermediate segments. Prominently and characteristically, the glomeruli are essentially normal in size and morphology. Although the vessels of the glomerular tufts are patent, the number of vessels seems to be reduced. Bowman's capsule and the space within it appear to be essentially normal, except that occasionally it may be dilated. The proximal tubule or the junction of the glomeruli with the tubules at the region of the Goormaghtigh body may exhibit mild histologic changes. This juxtaglomerular apparatus may be hypertrophied, with an increase in the granularity of the cells. The proximal convoluted tubules may appear essentially normal, although there is a tendency for the delicate brush-like border to be somewhat obliterated. There may be evidences of cloudy swelling, mild degeneration, and in rare cases, even necrosis. Within the lumen may be found precipitated material, which gives the appearance of concentrated proteins and stains with eosin. Heme casts are rarely observed at this level. This segment is readily damaged by mercury, uranium, or oxalates, but rarely is it damaged by the crushing injury in the lower nephron syndrome. This is also true to some extent in transfusion reaction, although in the latter there is usually more damage to the upper portion of the nephron than with crushing injuries.

The intermediate segment of the nephron is not ordinarily injured, although it may show changes such as described for the proximal portion, with accumulation of granular material and evidences of slight degeneration of epithelium.

The lower portion of the nephron, for which the term lower nephron nephrosis is applied, exhibits the greatest damage and seems to be selectively injured in the crush syndrome. Lower nephron damage is more apt to occur in cases of crush injury, burns, blood transfusion reactions, sulfonamide reactions, uteroplacental damage, and after excessive vomiting.

The morphologic changes observed microscopically are as follows: The damage occurs primarily in the tubular cells in the lower portion of the nephron. Degeneration varies from mild changes to complete patchy necrosis. Since the degeneration requires time to develop, its degree is relatively mild during the first 24 to 48 hours. Three to four days or more are required before definite evidences of degeneration appear. Since the lesions are characteristically patchy, there are scattered areas of desquamation of epithelium. Occasionally, pronounced lesions occur in the boundary zone, particularly at the point where the nephron is in close proximity to the vein.

These degenerative changes may result in bulging or even actual rupture of the necrotic portions into the veins. Diverticuli may be observed. Regeneration in various stages of development begins to make its appearance if survival time exceeds three or four days. There may be casting off of segments of epithelium with the growing of new cells beneath the dead lining. In the early stages the protoplasm tends to be basophilic and the nuclei stain intensely.

Healing takes place rapidly; if the patient survives 10 days, it is likely that the areas will be completely reëpithelized. Casts are the most characteristic and outstanding microscopic findings; they are usually of two kinds:

(1) Most conspicuous are the pigmented masses of heme substances which are found inspissated within the lumen of the lower portions of the nephrons. These are particularly highly developed when there is destruction of muscle and apparently have their origin from myohemoglobin or some of its derivatives. In hemolytic conditions, such as transfusion reactions, hemoglobin casts develop which are similar to the myoglobin casts following destruction of muscle. In unstained sections the casts have a reddish hue; when stained with hematoxylin and eosin, they are usually brownish or copper-colored, but the reaction for iron is negative.<sup>61</sup> The casts have a smooth and solid appearance and occasionally assume the form of spherules. They tend to accumulate in greatest numbers in the distal convoluted tubules but are larger in the wider collecting tubules. When they occur near thin-walled veins, they are apt to be prominent.

(2) Less conspicuous are those casts which are not pigmented and have the appearance of hyalin casts. They are stained faintly with eosin and look much like inspissated and coagulated protein material. Tending to occur in the region of the lower nephron where the injury is most severe, they give the impression of obstructing and blocking the flow of urine through the nephron.

Another interesting aspect of the microscopic pathologic changes is that seen in the interstitial tissues around the foci in the tubules showing extreme disintegration. Edema and inflammatory reactions are evident. There is an accumulation of inflammatory cells, particularly lymphocytes and histiocytes, whereas granulocytes are scanty and giant cells are rarely seen. Fibrosis usually develops at the end of a week, and if there is a great deal of destruction, scars appear. These areas may vary from relatively few to large numbers, depending upon the severity of the reaction. The interstitial changes are particularly pronounced in the boundary zone and at times in the cortex around the venous channels near the glomeruli. If necrosis is severe, casts are extruded into the stroma, producing local reactions. As stated previously, one of the interesting pathologic changes is found in the region of the large venous channel, especially in the boundary zone. There the veins are rather thin-walled and normally course near the renal tubules. When the tubules are damaged, the veins apparently bulge into the lumen.

In the presence of necrosis, the tubules may rupture into the vein and, spilling their contents therein, produce thrombosis. These thrombi rarely obstruct the vein. Remnants of epithelium may be found embedded in the thrombus. Veins are often infiltrated with inflammatory cells. Such venous lesions are usually encountered in patients who survive at least five days.

The collecting tubules rarely undergo any unusual degenerative changes. Their general appearance is normal, although heme casts are prominent at this level. They are often large and tend to fill and stretch the collecting tubules. Endothelial leukocytes may be found in this region. Some of the older lesions in patients surviving a long period of time show evidences of advanced degeneration of the heme compounds.

The number of nephrons involved, the extent of lesions, and evidences of obstruction vary considerably. Because of these histologic studies, it has been difficult for some to attribute oliguria primarily to obstruction.

#### THE MECHANISM OF THE LOWER NEPHRON SYNDROME

Although the exact mechanism for this syndrome is not known, certain facts have been established. Studies of Bywaters and his group concerned primarily with the crush syndrome indicate that crushed muscle undergoes characteristic changes within a short period of time. The muscle becomes ischemic due to direct compression which interferes with the blood supply and which probably is associated with sudden spasm and thrombosis, rupture or obstruction of the vessel. Following damage by crushing, the muscles become blanched, friable, and necrotic and resemble fish flesh. A sharp line of demarcation, which corresponds to the line of pressure, develops between the injured and uninjured areas. Muscles undergo various degrees of degeneration, varying from complete necrosis to almost normal tissue near the edge of the injury. Because of the edema, the muscles bulge through openings made in the fascia at operation. Some portions of the muscle may appear grossly normal, without too much pallor, but may still show isolated necrosis on microscopic section. This type of change is usually associated with arterial spasm, probably due to periarterial hemorrhage or rupture of the blood vessels from the crushing. Chemical studies of the necrotic muscle compared with undamaged muscle in the same individual, show that the damaged muscle has lost 75 per cent of its pigment, 75 per cent of the phosphorus, 66 per cent of the potassium, 70 per cent of the creatine, and 95 per cent of the acid-producing substances.<sup>16</sup> All of this is lost on the first day and therefore rapidly appears in these amounts in the urine; this means that the kidneys must excrete this large amount of material within an exceedingly short time. It is thought by many that this sudden loading of the kidneys with large amounts of probably toxic material for excretion may be responsible for the damage observed. These studies have been corroborated in experimental animals.

*The Rôle of the Heme Derivatives.* With destruction of muscle there is release of myoglobin.<sup>10, 15, 16, 20, 25, 61, 73, 111</sup> Hemoglobin is set free when

red cells are suddenly hemolyzed. When pigments are liberated in large quantities and cannot be metabolized in usual fashion by the liver to be excreted in the bile, they are excreted by the kidneys.<sup>2, 5, 39, 60, 72, 75, 112</sup> The mechanism by which the pigments reach the lumen of tubules is not clear. There are differences of opinion about the passage of hemoglobin molecules through the glomerular membranes. Since the molecular weight of hemoglobin is 68,000 and that of serum albumin is 70,000, it is considered by many observers to be unlikely that hemoglobin is able to pass through the glomerular membranes any more easily than serum albumin. However, several hypotheses have been presented to explain the mechanism by which hemoglobin enters the lumen of the nephron. One is that a small amount leaks through the glomeruli; a second is that some of the hemoglobin is broken into small components and is excreted as such; and a third is that damage to the tubules and glomeruli increases the permeability of these membranes to hemoglobin. None of these ideas is supported by sufficient direct data. As pointed out by Kreützer and his associates,<sup>57</sup> who reviewed the data on the excretion of hemoglobin and myoglobin in the urine in a study of spontaneous myohemoglobinuria, little is known about the details.

Myoglobin has a molecular weight of 17,500, or is about one-fourth the size of the hemoglobin molecule, and it contains one iron atom instead of four. Because of the presence of iron, the benzidine or guaiac test for occult blood in the urine of patients with myoglobinuria is positive. The diagnosis of myohemoglobinuria should be considered if the urine is dark and yields a positive test for occult blood, is free from red cells, and if no evidences of hemolytic disease exist. Since a minimum of about 20 mg. of hemoglobin per 100 c.c. of plasma has to be reached in order to give a reddish tinge to the plasma and since myoglobin has a renal threshold of about 20 mg. per 100 c.c. whereas that of hemoglobin is 100 mg., the color of the plasma aids in differential diagnosis. Therefore, it is possible to rule out hemoglobinuria, if a sample taken just before the appearance of dark urine does not exhibit a reddish tinge. Of course, myoglobin can be differentiated from hemoglobin and identified easily by means of ultracentrifugation, ultrafiltration and by spectroscopic examination. Myoglobinuria might be confused with acute porphyrinuria, but this is relatively unlikely since the porphyrins do not give a positive reaction to the benzidine or guaiac tests for occult blood. However, such problems are not troublesome in the presence of the lower nephron syndrome, since the other phases of the disease are distinct. The small size of the myoglobin molecule, the low renal threshold, and the rapid liberation of myoglobin from damaged muscle all contribute to the sudden overloading of the kidneys whenever there is crushing or damage to large masses of muscle. Apparently the low renal threshold is related to the molecular size of 17,500, which is small enough to permit passage through an unaltered glomerular membrane.

The heme compounds are apparently concentrated or precipitated in the lower part of the nephron. This is true of that derived from hemoglobin

and probably of the myoglobin derivative as well. When it passes through the glomerular filter, a small portion is reabsorbed by the cells of the proximal tubules.<sup>61</sup> As a result there is a concentration of the material in the cells lining the tubules. Furthermore, as the pigment passes through the tubules, there is a tendency for it to be precipitated and accumulated within the lumen of these tubules.

Several hypotheses have been introduced to explain the process of the pigment precipitation. It is thought that the pigment is removed from solution, probably as hematin, when the intratubular fluid becomes sufficiently acid, that is, has a pH below 6, and when simultaneously water is reabsorbed and the material is concentrated. Such requirements are met in the lower nephron and collecting tubules. By means of intravenous injections of myoglobin Bywaters and Stead<sup>21</sup> were able to produce renal failure if the acidity of the urine reached levels of a pH of 4.5 to 6.1. They were unable, however, to repeat some of these experiments. It is because of the influence of low pH on the precipitation of these pigments that alkalinizing measures are employed therapeutically.

It is also believed that cellular injury is concerned with *precipitation* of these pigments in the tubules. Renal damage produced by ischemia results in the precipitation of the pigments in the tubules.

It is also stated that inadequate urinary flow through the tubules, effected by the decreased blood pressure and volume of glomerular filtration, and increased tubular reabsorption lead to accumulation and retention of the pigment in the lumina of the tubules. By dissection, however, Oliver<sup>80</sup> found many nephrons without casts. It is difficult to understand why certain nephrons show an accumulation of these casts and pigment whereas others do not.

It has not been demonstrated that *myoglobin or hemoglobin is toxic*. However, there may be some degradative products or derivatives which are. Some observers are of the opinion that such toxic substances exist and react more readily in an acid medium. There are no data available to demonstrate the existence of any toxic effects from these pigments. It has been proposed by several observers that the damage produced by these pigments is due to the *obstruction*, though Oliver's sections and dissections failed to reveal complete obstruction as far as the tubules were concerned. Many others have confirmed his observation. Furthermore, the nephron above the level of the casts fails to show any evidences of severe dilatation, as in hydro-nephrosis.

Other observers contend that a *toxic substance* might arise from injured tissue. This has been maintained to be true in the case of the crush syndrome, in which *toxins* are liberated in the area of muscular injury, in instances of burns, uteroplacental injury, and after administration of some drugs, such as sulfonamides and mercury. Proof is lacking that degradative products are liberated in ischemic muscles or burned areas which damage

the kidney. It has also been suggested that *organic* and *inorganic substances*, such as uric acid, phosphoric acid, potassium and creatine, liberated by injured tissue or toxic states, contribute to the renal damage.<sup>9, 35, 50, 61, 64, 96</sup>

Still others have suggested that *proteolytic enzymes* liberated in injured tissue may be responsible for the damage to the renal tubules.<sup>76</sup> Associated vomiting, disturbances in electrolyte balance, malnutrition, and dehydration may contribute to the intoxication and damage of the kidneys.<sup>15, 16, 61</sup> Disturbances in blood volume and in fluid balance could conceivably contribute to reduction in renal function, although such ideas remain conjectural.

It has also been proposed that disturbances in renal blood flow, particularly in the presence of shock, are of paramount importance in diminishing renal function and in damaging the nephron.<sup>26, 32, 54, 59, 81, 88, 93, 98, 99, 102, 103</sup> It has been observed that in patients suffering from shock, particularly if it is severe and prolonged, more severe damage to the tubules is sustained. This, however, may not be directly related to the shock, the latter being only another manifestation of the severity of the general injury. It is likely that all of the facts mentioned play some rôle, though the exact mechanism and the contributing rôle of each individual factor is not yet clear.

The mechanism by which oliguria develops is likewise unknown. Several hypotheses have been presented: (1) That it is due to a disturbance in glomerular filtration, which is the result of impairment of renal circulation.<sup>4, 29, 37, 49, 53, 67, 71, 85, 91, 92, 95</sup> This is related to the idea advanced by Trueta and his associates<sup>100</sup> of "shunting" of the renal circulation from the cortical portion of the kidneys to the medulla. It may be partially attributable to peripheral circulatory collapse and shock which impair glomerular filtration. (2) That oliguria results from tubular obstruction, which interferes with the rate of urinary flow. However, more and more observers are rejecting this concept. (3) That oliguria is incident to the disturbance in tubular reabsorption as a result of tubular damage from an impairment of renal circulation, a theory proposed by Phillips and coworkers<sup>53, 85</sup> and by others. The damaged areas, that is, the lower tubular portions of the nephron, become essentially parchment paper as far as selectivity of reabsorption is concerned.<sup>15, 16, 53, 61, 85</sup> Since there is no selective reabsorption, absorption of glomerular filtrate is complete qualitatively and almost quantitatively.<sup>87</sup> Consequently, the glomerular filtrate passes down the tubules and diffuses unaltered back into the circulation, so that there is almost complete reabsorption of the glomerular filtrate in its native state. This results in the formation of urine with approximately the same specific gravity as that of the glomerular filtrate, a value of 1.010. Lucké<sup>61</sup> and others are of the opinion that this almost complete leaking of glomerular filtrate through damaged tubular walls back into circulation is the best hypothesis to explain the histologic and clinical data of the lower nephron syndrome.

There are also many extrarenal factors concerned with the toxic picture. For example, anuria and azotemia will produce intoxication. Vomiting,



dehydration, hemorrhage, local injury, shock, and toxic materials, such as sulfonamides, mercury and products of infections, all make important contributions to the general clinical picture observed in the syndrome.

### THE URINE AND THE RENAL FUNCTION

After crushing injury, the first urine is usually acid and is brown because of the pigment of acid hematin.<sup>15, 16, 61, 74</sup> The mistaken idea that this indicates the presence of erythrocytes is disproved by microscopic examination. The supernatant urine may be normal in color but is usually smoky. If the pH approaches neutrality, the urine tends to be red with little or no sediment. The first urine passed after injury is rarely normal because, as mentioned previously, the release and excretion of myoglobin or hemoglobin is extremely rapid. When the systolic blood pressure drops below 70 or 80 mm. of mercury, little urine is excreted.

The pigment in the urine usually shows a broad band in the red zone, signifying a metmyoglobin compound, as well as two bands in the yellow-green portion, which closely resemble those of oxyhemoglobin. Excretion of pigment begins to decrease in one to two days, and casts start to appear in the urine in large quantities. At first, they are pigmented casts or aggregations of pigmentary granules formed in the casts; these become stringy, and at the end of the first week the pigment core is covered by layers of desquamating epithelial cells. Occasionally the casts found later in the disease may be entirely cellular. It is at this time, as indicated in the discussion on pathology, that cellular desquamation and new growth reach their maxima. The amount of urine excreted decreases progressively and during the first week may reach values of 25 to 50 c.c. in 24 hours. The composition of the urine resembles that of glomerular filtrate. The concentration of urea is low, often less than 1 gm. per 100 c.c., whereas the blood urea may be as high as 300 mg. per c.c. Chloride concentration tends to be high in the urine despite lower than normal blood concentration. Reducing substances are occasionally found in small amounts, and potassium and creatine are present in abnormally large quantities. This, of course, is particularly true when the crushing syndrome causes extensive muscular damage.

Nitrogen retention is associated with the decrease in renal function. The patient begins to exhibit drowsiness with the development of uremia. As stated previously, the blood chloride level tends to fall, and the carbon dioxide combining power declines, due to liberation of lactic acid and other inorganic acids from the damaged tissue and loss of normal acid base regulatory function of the kidneys.

There have been a number of studies recently on the effect of hemorrhage, shock and crushing injury on renal function. Van Slyke and his associates,<sup>102</sup> for example, found that hemorrhage produced experimentally in dogs causes severe vasoconstriction associated with the drop in blood volume. This maintains glomerular filtration, provided that the vasocon-

striction does not selectively involve the cortical portions of the kidney. When shock progresses so that the blood pressure reaches extremely low values, the filtration pressure is decreased and the quantity of glomerular filtrate becomes reduced. Corcoran, Taylor and Page<sup>26</sup> found a decrease in renal blood flow due almost entirely to an increase in renal vascular resistance in dogs following release of the tourniquets in "tourniquet-produced" shock. This is brought about by the increase in blood viscosity and by vasoconstriction of the afferent and efferent glomerular arterioles. Pain is of little influence, as blocking of sympathetic nerves has no effect upon renal function. Apparently, therefore, vasoconstriction is humoral in origin.

Phillips and his associates<sup>53, 85</sup> have shown that ischemia produced by gently clamping the renal arteries will interfere especially with tubular function. The main effect is to decrease selective absorption of the tubules so that glomerular filtrate is absorbed almost completely, the tubules becoming essentially parchment membranes, instead of living membranes with ability to absorb selectively. Similar observations have been made by Badenoch and Darmady.<sup>4</sup> These latter authors were able to produce disturbances in the distal segments, including patchy necrosis similar to that described by Bywaters<sup>15</sup> and Lucké.<sup>61</sup> Apparently, there was correlation between the histologic picture and disturbances in renal function.

*Sequelae.* The fatality rate is extremely high, the survival rate varying between 10 and 33 per cent. As far as is known, those who survive apparently do not experience residual disturbances in renal function, although it is not clear from published reports whether or not adequate follow-up studies have been conducted. A prolonged follow-up period would be required to ascertain the residual renal state. It is well to bear in mind when estimating morbidity that patients with the most severe damage die whereas those with the least survive; therefore, a follow-up of renal function would necessarily include only those with mild damage. With improvement in therapeutic methods, increased survival rate of the more seriously ill patient will result, thus permitting better evaluation of the problem of morbidity, particularly if follow-up studies are emphasized.

## TREATMENT

Before a discussion is undertaken of the management of the patient in whom the syndrome has developed, it is necessary to point out that there are certain types of the lower nephron syndrome which can be readily prevented. Most transfusion reactions are avoidable, being due entirely to carelessness. The same is true of intoxications, especially sulfonamides; more care in the selection of patients and during administration should reduce the incidence of injury from sulfonamides. Furthermore, when the slightest evidence of damage appears, immediate discontinuance of these drugs will usually result in minimal injury. It is the neglected patients who sustain the greatest damage. Uteroplacental damage with the complicating lower nephron syn-

drome has been reduced by more adequate care of the problems of pregnancy and the control of criminal abortion. The same is true for accidents and burns as well as the control of intoxications from mercury. A study of the incidence of the lower nephron syndrome reveals that most cases encountered in civilian practice are preventable and are usually the result of negligence.

Once the patient has had an injury or a reaction which is known to produce lower nephron nephrosis, steps should be taken immediately to *prevent* its development. These measures are based in part upon physiologic phenomena concerned with sudden liberation of myoglobin or hemoglobin in the plasma and consist in immediate hospitalization of the patient, with careful attention and nursing. Fluids should be administered in quantities sufficient to maintain diuresis. Alkali, such as sodium bicarbonate, should be given to maintain an alkaline urine, determined not by an arbitrary dose but by the simple expedient of red litmus dropped into the urine. These patients should be carefully watched so that oliguria may be noted immediately, since the administration of alkali and fluids is governed by the output. Overloading with fluid is dangerous<sup>97</sup> and may lead to pulmonary edema. Intake and output of fluid should be charted carefully. The patient should be examined frequently for evidences of edema, and the changes in blood chemical values should be followed closely. Patients such as those who have had severe burns or those who have been severely injured by compression must be under close observation for the possibility of shock. Should it develop, the usual therapeutic measures should be employed, including the use of either whole blood or plasma. It is stated that loss of great quantities of fluid into large masses of injured tissues may result in oligemic shock. Blood volume must therefore be maintained, but therapy must be based upon objective data, derived from the usual laboratory procedures, including hematocrit, blood count, and blood protein and serum chloride determinations. Such studies may permit early recognition of shock or predisposition to it. The blood pressure, of course, should be recorded at frequent intervals. If hemorrhage occurs, it is necessary to replace the lost blood.

Morphine should be given for pain and the patient should be made comfortably warm but should not be overheated. Local surgical treatment of the injured areas should be given adequate attention. It has been suggested that the parts should be immobilized and the limb cooled with icebags in order to decrease the rate of autolysis and absorption of toxic materials. This cooling process has been reported to be successful in the hands of some but not all. If there is considerable pressure in the region of large vessels and it is thought that this tension is resulting in obstruction, splitting of fascia by means of incisions made along the course of the vessels of the limbs has been recommended but is not generally advocated. Casts, if employed, should be applied carefully and observed closely, since constriction resulting from development of edema with increase in volume of the part may result in further arterial obstruction. Obviously, it is important to avoid constricting bandages.<sup>10</sup>

The rôle of sympathetic blocking or sympathectomy is yet to be evaluated. Amputation should be performed if the part is definitely useless but unless it is done within the first 24 hours, postponement may be necessary, particularly if renal damage is serious.<sup>16</sup> Under such conditions, splinting and physical therapy should be employed until amputation can be performed.

Once renal failure, with oliguria and progressive uremia, develops, relatively little can be done except for the use of some of the more experimental procedures now under investigation, such as the artificial kidney or dialysis. It has been suggested that fluids should be administered to these patients in the presence of anuria and oliguria. However, it is well to remember that large quantities of fluids may produce severe edema and increase the damage. Sodium lactate, 5 per cent glucose, and sodium chloride may be used in amounts governed as much as possible by studies of the blood chemistry and by the clinical state. Human Ringer's solution may also be used. It is possible to administer fluids by means of gastric or duodenal tubes if the patient is not vomiting excessively; otherwise, intravenous medication must be employed. Fluids should not be administered to any extent beyond that which produces slight edema; in these amounts fluids might dilute the toxins and at the same time produce diuresis once renal function begins. Mercurial diuretics and decapsulation have been advocated, but it is unlikely that the latter is of any value. If results are not obtained promptly with mercurial diuretics, they should be discontinued. However, in view of the nature of the lesions and the mechanism of action of mercurials, it is likewise unlikely that these would be of great value—in fact, actual increased damage might result. One or two doses will probably be accompanied by no deleterious effects.

*The Artificial Kidney.* There has been increased interest in the use of artificial methods for eliminating metabolites. These procedures are based upon the principle that a method, even if crude, which would eliminate toxic substances during acute renal failure might prolong life long enough to permit renal repair and return of renal function. This idea is not a new one; it was advocated as early as 1923.<sup>44, 52, 79</sup> A number of papers have been published suggesting this procedure or peritoneal lavage: that of Ganter<sup>44</sup> in 1923, Landsberg and Gnoinski<sup>58</sup> in 1925, Rosenak and Siwon<sup>90</sup> in 1926, Bliss, Kastler and Nadler<sup>11</sup> in 1932, Haam and Fine<sup>51</sup> in 1932, Rhoads<sup>80</sup> in 1938, Balazs and his associates<sup>6</sup> in 1934, Wear, Sisk and Trinkle<sup>106</sup> in 1938, Fine, Frank and Seligman<sup>40</sup> in 1946, Buckley and Scholten<sup>13</sup> in 1947, and Basset and coworkers<sup>7</sup> in 1947.

The method of peritoneal lavage consists in placing a catheter in an upper lateral abdominal quadrant and another in the lower contralateral abdominal quadrant and running a large quantity of a modified Tyrode's solution through the peritoneal cavity. This is done continuously, 18 to 24 liters being used in 24 or 48 hours. The formulae for these solutions may be found in the aforementioned papers describing the technic. These solutions have sulfadiazine, heparin, and penicillin added in order to prevent

clotting and infection. When the physician is interested in removing fluid from the body, the solution is made slightly hypertonic by increasing the amount of glucose, and when it is desired to administer fluid through the peritoneum, the solution is made hypotonic by decreasing the concentration of the glucose. Fibrin usually forms in sufficiently large quantities to obstruct the flow of the fluid. Disturbances in bowel function, such as ileus, nausea, vomiting and abdominal distention and pain, frequently develop. Peritoneal lavage is not a satisfactory procedure; most patients treated by this method have died.

Another method consists in the use of the *artificial kidney*. Circulating substances in the blood which are diffusable are removed by dialysis through a dialyzing membrane.<sup>1, 52, 78, 79</sup> Probably the first paper suggesting this method is that of Abel, Rowntree and Turner,<sup>1</sup> published in 1914; they studied dogs and suggested that the same procedure might be applied to man. Their apparatus consisted of many dichotomously branching dialyzing tubes submerged in a dialyzing fluid. After a period of dialysis the blood is returned to the animal. Kolff<sup>56</sup> in 1944, described an artificial kidney which consisted of a large drum upon which 40 to 45 yards of visking cellulose tubing were wound in spiral fashion. The drum rotates, passing the cellulose tubing through a tray of dialyzing fluid. Blood from the patient enters from an artery into one end of the tubing and is returned to a vein from the other end. By means of gravity, the blood is made to progress down this spiral tube for dialysis. More recently others have begun to modify Kolff's technic. A few patients have been saved by means of this artificial kidney. As much as 120 liters of blood have been made to flow through the artificial kidney. One or several treatments may be given, depending upon the condition of the patient and the success of each treatment. As much as 263 gm. of urea have been removed, and in one patient, for example, blood urea declined from 704 to 192 mg. per 100 c.c. Usually if dialysis is attempted for the second time and results are not satisfactory, it is not repeated. Kolff and his associates are still studying this problem.

More recently, *gastric lavage* has been advocated during the period of oliguria to eliminate retained products of metabolism. The paper of Vermooten and Hare<sup>104</sup> suggested gastric lavage with the use of a special gastric tube, preferably with two lumina, a duplex afferent and efferent tube. Two separate tubes are less satisfactory, since it is not possible to be certain of the relative positions of the openings of the separate afferent and efferent tubes. The method of gastric lavage consists in continuously irrigating the stomach with about 10 liters of a special irrigating fluid over a period of 24 hours. The rate of irrigation is about 150 drops per minute. These authors have been able to remove some urea by this technic. It was not possible to evaluate properly the precise effect of the procedure in their patient. However, it is a procedure which deserves further investigation.

Rogers, Sellers and Gornall<sup>89</sup> suggested the use of *intestinal irrigation* in the treatment of acute uremia, oliguria or anuria. These authors used a

triple-bore, thin-walled rubber tube with a small balloon at its tip. In experimental animals, the tube was passed various distances down the intestinal tract, the balloon was inflated and the intestinal tract was irrigated with the perfusion fluid. Warm physiologic saline solution was used. The observers were able to reduce azotemia from 198 to 126, from 198 to 112, from 231 to 145 mg. per 100 c.c. in separate animals, using 12 to 18 liters of fluid over a period of about six hours. They found that the return rinsing fluid contained from 4.3 to 5.4 gm. of nonprotein nitrogen. This idea is essentially the same as gastric lavage but should be more promising because of the more rapid diffusion of materials and greater diffusion areas. Further investigations are definitely indicated.

As indicated by all investigators, if the patient survives the period of acute uremia and the acute disease so that repair may take place, diuresis would be established in many severely injured patients. The percentage of patients who sustain serious damage and who will again produce urine is undetermined. There must be some limit to the degree of damage and the ability for repair. Postmortem studies have indicated that if some of the patients had been able to survive a few more days, it is likely that renal function would have returned to normal. The therapeutic problem is to prolong life during a brief critical period. General hospitals with proper laboratory facilities and trained personnel should be prepared to employ the new procedures previously described, which promise to be life saving.

*General Therapeutic Measures.* It is important to remember that certain general measures must be emphasized in the management of these patients. Most important of all is *good nursing*. The patient should have constant attention, particularly when he is having his greatest difficulty. He should be made mentally as well as physically comfortable, since he is apt to become apprehensive and anxious about his disease. Most patients know they are seriously ill and are aware of the fact that they are likely to die.

Attention to electrolyte balance, fluids, vitamins, and nutrition should be emphasized. If possible, a large portion of the necessary fluids and carbohydrates should be given by gastric or duodenal tube. Protein intake should be held to a minimum during the time of renal failure, for the metabolism of administered proteins will only increase the rate of accumulation of non-protein nitrogen and toxic protein substances.

Borst<sup>12</sup> has found that a diet low or absent in protein, consisting almost entirely of fat and carbohydrate, is of considerable value in the management of acute renal insufficiency. Some of his patients were fed a diet consisting of 150 gm. of butter and 200 gm. of sugar, a total of 2,000 calories. This yields practically no protein and little potassium and phosphorus. Patients have received this diet for over three consecutive weeks, except for variations in quantity, without difficulty and with great benefit during periods of uremia. Contrary to most opinions, severe-to-complete restriction of proteins in the diet reduces protein catabolism to extremely low levels, so that by the end of three days the daily nitrogen excretion is less than 6 gm., and

less than 4 gm. daily by the end of 14 days. By the end of three days the potassium excretion is about 30 mEq. per day and 10 mEq. by the end of 14 days. Another diet prepared by Borst, a gruel consisting of 1.5 liters of water, 100 gm. of custard powder, 150 gm. of sugar and 100 gm. of butter and providing 1,750 calories, has been found useful in the cases under discussion.

During the period of recovery, the food intake should be calculated so as not to overburden the kidneys until they have made complete recovery. Proteins, particularly animal proteins, must not be administered in large quantities. To evaluate the completeness of recovery, repeated studies of renal function, including Addis counts, should be made. Defects in renal function may persist for many months, if not permanently, and may require appropriate regulation of the patient's regime.

#### BIBLIOGRAPHY

1. ABEL, J. J., ROWNTREE, L. G., and TURNER, B. B.: On the removal of diffusible substances from the circulating blood of living animals by dialysis, *Jr. Pharmacol. and Exper. Therap.*, 1914, v, 275-316.
2. ANDERSON, W. A. D., MORRISON, D. B., and WILLIAMS, E. F., JR.: Pathologic changes following injections of ferrihemate (hematin) in dogs, *Arch. Path.*, 1942, xxxiii, 589-602.
3. AYER, G. D., and GAULD, A. G.: Uremia following blood transfusion; nature and significance of renal changes, *Arch. Path.*, 1942, xxxiii, 513-532.
4. BADENOCH, W. W., and DARMADY, E. M.: The effects of temporary occlusion of the renal artery in rabbits and its relationship to traumatic uraemia, *Jr. Path. and Bact.*, 1947, lix, 79-94.
5. BAKER, S. L., and DODDS, E. C.: Obstruction of the renal tubules during excretion of haemoglobin, *Brit. Jr. Exper. Path.*, 1925, vi, 247-260.
6. BALAZS, JULIUS, and ROSENAK, STEPHAN: Zur Behandlung der Sublimatanurie durch peritoneale Dialyse, *Wien. klin. Wchnschr.*, 1934, xlvii, 851-854.
7. BASSET, S. H., BROWN, H. R., KEUTMANN, E. H., HOLLER, JACOB, VAN ALSTINE, HELEN E., MOCEJUNAS, OLGA, and SCHANTZ, HELEN: Nitrogen and fluid balance in treatment of acute uremia by peritoneal lavage, *Arch. Int. Med.*, 1947, lxxx, 616-636.
8. BEALL, D., BYWATERS, E. G. L., BELSEY, R. H. R., and MILES, J. A. R.: Case of crush injury with renal failure, *Brit. Med. Jr.*, 1941, i, 432-434.
9. BIELSCHÖWSKY, M., and GREEN, H. N.: Shock-producing factor(s) from striated muscle; II. Fractionation, chemical properties and effective doses, *Lancet*, 1943, ii, 153-155.
10. BING, R. J.: The effect of hemoglobin and related pigments on renal functions of the normal and acidotic dog, *Bull. Johns Hopkins Hosp.*, 1944, lxxiv, 161-176.
11. BLISS, S., KASTLER, A. O., and NADLER, S. B.: Peritoneal lavage. Effective elimination of nitrogenous wastes in absence of kidney function, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxix, 1078-1079.
12. BORST, J. G. G.: The cause of hyperchloremia and hyperazotemia in patients with recurrent massive hemorrhage from peptic ulcer, *Acta med. Scandinav.*, 1938, xcvi, 68-88.
13. BUCKLEY, R. W., and SCHOLTEN, R. A.: Treatment of acute uremia by peritoneal lavage, *New England Jr. Med.*, 1947, ccxxxvii, 431-434.
14. BURCH, G. E., and WINSOR, T.: Renal damage following the use of sulfathiazole, *New Orleans Med. and Surg. Jr.*, 1942, xciv, 474-481.

15. BYWATERS, E. G. L.: War medicine series; crushing injury, *Brit. Med. Jr.*, 1942, ii, 643-646.
16. BYWATERS, E. G. L.: Ischemic muscle necroses; crushing injury, traumatic edema, the crush syndrome, traumatic anuria, compression syndrome: a type of injury seen in air raid casualties following burial beneath debris, *Jr. Am. Med. Assoc.*, 1944, cxxiv, 1103-1109.
17. BYWATERS, E. G. L., and BEALL, D.: Crush injuries with impairment of renal function, *Brit. Med. Jr.*, 1941, i, 427-432.
18. BYWATERS, E. G. L., DELORY, G. E., RIMINGTON, CLAUDE, and SMILES, JOHN: Myohemoglobin in the urine of air raid casualties with crushing injury, *Biochem. Jr.*, 1941, xxxv, 1164-1168.
19. BYWATERS, E. G. L., and DIBLE, J. H.: Renal lesion in traumatic anuria, *Jr. Path. and Bact.*, 1942, liv, 111-120.
20. BYWATERS, E. G. L., and DIBLE, J. H.: Acute paralytic myohaemoglobinuria in man, *Jr. Path. and Bact.*, 1943, lv, 7-15.
21. BYWATERS, E. G. L., and STEAD, J. K.: Production of renal failure following injection of solutions containing myohaemoglobin, *Quart. Jr. Exper. Physiol.*, 1944, xxxiii, 53-70.
22. BYWATERS, E. G. L., and others: Discussion on the effects on the kidney of trauma to parts other than the urinary tract, including crush syndrome, *Proc. Roy. Soc. Med.*, 1942, xxxv, 321-339.
23. COLMERS, DR.: Ueber die durch das Erdbeben in Messina am verursachten Verletzungen, *Arch. f. klin. Chir.*, 1909, xc, 701-747.
24. CORCORAN, A. C., and PAGE, I. H.: Effects of hypotension due to hemorrhage and of blood transfusion on renal function in dogs, *Jr. Exper. Med.*, 1943, lxxviii, 205-224.
25. CORCORAN, A. C., and PAGE, I. H.: Renal damage from ferroheme pigments, myoglobin, hemoglobin, hematin, *Texas Rep. Biol. and Med.*, 1945, iii, 528-544.
26. CORCORAN, A. C., TAYLOR, R. D., and PAGE, I. H.: Immediate effects on renal function of the onset of shock due to partially occluding limb tourniquets, *Ann. Surg.*, 1944, cxviii, 871-886.
27. DAMON, S. R.: Food infections and food intoxications, 1928, Williams and Wilkins Co., Baltimore.
28. DANIELS, W. B., LEONARD, B. W., and HOLTZMAN, S.: Renal insufficiency following transfusion; report of 13 cases, *Jr. Am. Med. Assoc.*, 1941, cxvi, 1208-1215.
29. DARMADY, E. M.: Renal anoxia and the traumatic uraemia syndrome, *Brit. Jr. Surg.*, 1947, xxxiv, 262-271.
30. DARMADY, E. M., SIDONS, A. H. M., CORSON, T. C., LANGTON, C. D., VITEK, Z., BADENOCH, A. W., and SCOTT, J. C.: Traumatic uraemia, reports on 8 cases, *Lancet*, 1944, ii, 809-812.
31. DEGOWIN, E. L., WARNER, E. D., and RANDALL, W. L.: Renal insufficiency from blood transfusion; anatomic changes in man compared with those in dogs with experimental hemoglobinuria, *Arch. Int. Med.*, 1938, lxi, 609-630.
32. DOLE, V. P., EMERSON, J., JR., PHILLIPS, R. A., HAMILTON, P., and VAN SLYKE, D. D.: The renal extraction of oxygen in experimental shock, *Am. Jr. Physiol.*, 1946, cxlv, 337-345.
33. DOUGLAS, J. W. B.: Incidence of signs of renal injury following prolonged burial under debris in an unselected series of 764 air-raid casualties admitted to hospital, *Brit. Jr. Urol.*, 1945, xvii, 142-147.
34. DUNN, J. S., HAWORTH, A., and JONES, N. A.: Pathology of oxalate nephritis, *Jr. Path. and Bact.*, 1924, xxvii, 299-318.
35. DUNN, J. S., and POLSON, C. J.: Experimental uric acid nephritis, *Jr. Path. and Bact.*, 1926, xxix, 337-352.
36. EDWARDS, J. G.: The renal tubule (nephron) as affected by mercury, *Am. Jr. Path.*, 1942, xviii, 1011-1027.



37. EGGLETON, M. G., RICHARDSON, K. C., SCHILD, H. O., and WINTON, R. R.: Renal damage due to crush injury and ischaemia of limbs of anaesthetized dog, *Quart. Jr. Exper. Physiol.*, 1943, xxxii, 89-106.
38. ERB, I. H., MORGAN, E. M., and FARMER, A. W.: Pathology of burns, pathologic picture as revealed at autopsy in series of 61 fatal cases treated at Hospital for Sick Children, Toronto, Canada, *Ann. Surg.*, 1943, cxvii, 234-255.
39. FAIRLEY, N. H.: Fate of extracorporeal circulating haemoglobin, *Brit. Med. Jr.*, 1940, ii, 213-217.
40. FINE, J., FRANK, H. A., and SELIGMAN, A. M.: The treatment of acute renal failure by peritoneal irrigation, *Ann. Surg.*, 1946, cxxiv, 857-878.
41. FOY, H., ALTMANN, A., BARNES, II. D., and KONDI, A.: Anuria, with special reference to renal failure in blackwater fever, incompatible transfusions, and crush injuries, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1943, xxxvi, 197-238.
42. FOY, H., GLUCKMAN, J., and KONDI, A.: Pigment metabolism and renal failure in acute sulphonamide haemolysis resembling blackwater fever, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1944, xxxvii, 303-319.
43. FRENCH, A. J.: Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfonamide chemotherapy, *Am. Jr. Path.*, 1946, xxii, 679-701.
44. GANTER, G.: Ueber die Beseitigung giftiger Stoffe aus dem Blute durch Dialyse, *Munchen. med. Wchnschr.*, 1923, lxx, 1478-1480.
45. GILLIGAN, D. R., ALTSCHULE, M. D., and KATERSKY, E. M.: Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions, *Jr. Clin. Invest.*, 1941, xx, 177-187.
46. GILLIGAN, D. R., and BLUMGART, H. L.: March hemoglobinuria; studies of clinical characteristics, blood metabolism and mechanism, with observations on 3 new cases, and review of literature, *Medicine*, 1941, xx, 341-395.
47. GOLLAN, K. R., LEMBERG, R., and MONEY, R. A.: Observations upon "crush injury" syndrome and Volkmann's contracture associated with severe brain injury and hyperthermia, *Med. Jr. Australia*, 1945, ii, 212-214.
48. GOODPASTOR, W. E., LEVENSON, S. M., TAGNON, H. J., LUND, C. C., and TAYLOR, F. H. L.: Clinical and pathologic study of kidney in patients with thermal burns, *Surg., Gynec. and Obst.*, 1946, lxxxii, 652-670.
49. GOORMAGHTIGH, N.: Vascular and circulatory changes in renal cortex in anuric crush-syndrome, *Proc. Soc. Exper. Biol. and Med.*, 1945, lix, 303-305.
50. GREEN, H. N.: Shock-producing factor(s) from striated muscle. I. Isolation and biological properties, *Lancet*, 1943, ii, 147-153.
51. HAAM, E. V., and FINE, A.: Effect of peritoneal lavage in acute uremia, *Proc. Soc. Exper. Biol. and Med.*, 1932, xxx, 396-398.
52. HAAS, GG.: Dialysieren des Stromenden Blutes am Lebenden, *Klin. Wchnschr.*, 1923, ii, 1888.
53. HAMILTON, P., PHILLIPS, R. A., and HILLER, A.: Duration of renal ischemia required to produce uremia, *Am. Jr. Physiol.*, 1948, clii, 517-522.
54. KEELE, C. A., and SLOME, D.: Renal blood flow in experimental "crush syndrome," *Brit. Jr. Exper. Path.*, 1945, xxvi, 151-159.
55. KOLFF, W. J.: Artificial kidney, *Jr. Mt. Sinai Hosp.*, 1947, xiv, 71-79.
56. KOLFF, W. J., and BERK, H. R. J.: The artificial kidney; a dialyzer with great area, *Acta med. Scandinav.*, 1944, cxvii, 121-134.
57. KREUTZER, F. L., STRAIT, L., and KERR, W. J.: Spontaneous myohemoglobinuria in man *Arch. Int. Med.*, 1948, lxxxix, 249-259.
58. LANDSBERG, M., and GNOINSKI, H.: Diffusion of urea in peritoneum in vivo, *Compt. rend. Soc. de biol.*, 1925, xciii, 787-788.
59. LAUSON, H. D., BRADLEY, S. E., and COUNNAND, A.: Renal circulation in shock, *Jr. Clin. Invest.*, 1944, xxiii, 381-402.

60. LOUW, ASGER, and NIELSEN, HOLGER E.: Paroxysmal paralytic hemoglobinuria, *Acta med. Scandinav.*, 1944, cxvii, 424-436.
61. LUCKÉ, B.: Lower nephron nephrosis, *Mil. Surg.*, 1946, xcix, 371-396.
62. LUETSCHER, J. A., JR., and BLACKMAN, S. S., JR.: Severe injury to kidneys and brain following sulfathiazole administration; high serum sodium and chloride levels and persistent cerebral damage, *Ann. Int. Med.*, 1943, xviii, 741-756.
63. LUND, C. C., GREEN, R. W., TAYLOR, F. H. L., and LEVENSON, S. M.: Burns, collective review, *Internat. Abstr. Surg.*, 1946, lxxxii, 443-478, in *Surg., Gynec. and Obst.* (June) 1946.
64. McFARLANE, D.: Experimental phosphate nephritis in rat, *Jr. Path. and Bact.*, 1941, lii, 17-24.
65. McLEITCHIE, N. G. B.: Renal lesions in case of excessive vomiting, *Jr. Path. and Bact.*, 1943, lv, 17-22.
66. MAEGRAITH, B. G., and FINDLAY, G. M.: Oliguria in blackwater fever, *Lancet*, 1944, ii, 403-404.
67. MAEGRAITH, B. G., HARVARD, R. E., and PARSONS, D. S.: Renal syndrome of wide distribution induced possibly by renal anoxia, *Lancet*, 1945, ii, 293-296.
68. MALAMUD, N., HAYMAKER, W., and CUSTER, R. P.: Heat stroke; clinicopathologic study of 125 fatal cases, *Mil. Surg.*, 1946, v, 397-449.
69. MALLORY, T. B.: Hemoglobinuric nephrosis in traumatic shock, *Am. Jr. Clin. Path.*, 1947, xvii, 427-443.
70. MANN, F. C.: Peripheral origin of surgical shock, *Bull. Johns Hopkins Hosp.*, 1914, xxv, 205-212.
71. MARSHALL, E. K., JR., and CRANE, M. M.: The influence of temporary closure of the renal artery on the amount and composition of the urine, *Am. Jr. Physiol.*, 1923, lxi, 387-403.
72. MASON, J. B., and MANN, F. C.: Effect of hemoglobin on volume of kidney, *Am. Jr. Physiol.*, 1931, xcvi, 181-185.
73. MILLIKAN, G. A.: Muscle hemoglobin, *Physiol. Rev.*, 1939, xix, 503-523.
74. MINAMI AUS TOKIO, DR. SEIGO: Über Nierenveränderungen nach Verschüttung, *Virchow's Arch. f. path. Anat.*, 1923, ccxlv, 247-267.
75. MINETT, F. C.: Haemoglobinurias and myoglobinurias of animals, *Proc. Roy. Soc. Med.*, 1935, xxviii, 672-678.
76. MIRSKY, I. A., and FREIS, E. D.: Renal and hepatic injury in trypsin "shock," *Proc. Soc. Exper. Biol. and Med.*, 1944, lvii, 278-279.
77. MURPHY, F. D., KUZMA, J. F., POLLEY, T. Z., and GRILL, J.: Clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, *Arch. Int. Med.*, 1944, lxxiii, 433-443.
78. MURRAY, GORDON, DELORME, EDMUND, and THOMAS, NEWELL: The artificial kidney, *Jr. Am. Med. Assoc.*, 1948, cxxxvii, 1596-1599.
79. NECHELES, HEINRICH: Über Dialysieren des Stromenden Blutes am Lebenden, *Klin. Wchnschr.*, 1923, ii, 1257.
80. OLIVER, JEAN: When seeing is believing, *Stanford Med. Bull.*, 1948, vi, 7-12.
81. OLSON, W. H., WALKER, L., and NECHELES, H.: Study of anuria in experimental shock, *Proc. Soc. Exper. Biol. and Med.*, 1944, lvi, 64-67.
82. PAGE, I. H.: Occurrence of vasoconstrictor substance in blood during shock induced by trauma, hemorrhage and burns, *Am. Jr. Physiol.*, 1943, cxxxix, 386-398.
83. PAGE, I. H., and ABELL, R. G.: State of vessels of mesentery in shock produced by constricting limbs and behavior of vessels following hemorrhage, *Jr. Exper. Med.*, 1943, xxvii, 215-232.
84. PAXSON, N. F., GOLUB, L. J., and HUNTER, R. M.: Crush syndrome in obstetrics and gynecology, *Jr. Am. Med. Assoc.*, 1946, cxxxi, 500-504.
85. PHILLIPS, R. A., and HAMILTON, P. B.: Effect of 20, 60 and 120 minutes of renal ischemia on glomerular and tubular function, *Am. Jr. Physiol.*, 1948, clii, 523-530.

86. RHOADS, J. E.: Peritoneal lavage in treatment of renal insufficiency, *Am. Jr. Med. Sci.*, 1938, cxcvi, 642-647.
87. RICHARDS, A. N.: Direct observations of change in function of the renal tubule caused by certain poisons, *Trans. Assoc. Am. Phys.*, 1929, xlv, 64-67.
88. RICHARDS, D. W., JR.: Circulation in traumatic shock in man, Harvey lecture (Feb. 17) 1944, *Bull. New York Acad. Med.*, 1944, xx, 363-393.
89. ROGERS, J. W., SELLERS, E. A., and GORNALL, A. G.: Intestinal perfusion in the treatment of uremia, *Science*, 1947, cvi, 108.
90. ROSENAK, S., and SIWON, P.: Peritoneal excretion of substances which otherwise are excreted in urine, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1926, xxxix, 391-408.
91. SCARFF, R. W., and KEELE, C. A.: Effects of temporary occlusion of renal circulation in rabbit, *Brit. Jr. Exper. Path.*, 1943, xxiv, 147-149.
92. SELKURT, EWALD E.: Changes in renal clearances following complete ischemia of the kidney, *Am. Jr. Physiol.*, 1945, cxliv, 395-403.
93. SHORR, E., ZWEIFACH, B. W., and FURCHGOTT, R. F.: On occurrence, sites and modes of origin and destruction, of principles affecting compensatory vascular mechanisms in experimental shock, *Science*, 1945, cii, 489-498.
94. SOBIN, S. S., ARONBERG, L. M., and ROLNICK, H. C.: Nature of renal lesion with sulfonamides and its prevention with urea, *Am. Jr. Path.*, 1943, xix, 211-223.
95. STARR, I., JR.: Production of albuminuria by renal vasoconstriction in animals and in man, *Jr. Exper. Med.*, 1926, xliii, 31-51.
96. STONER, H. B., and GREEN, H. N.: Adenosine compounds and phosphates in blood of shocked rabbits, *Jr. Path. and Bact.*, 1944, lxvi, 343-354.
97. STRAUSS, M. B.: Acute renal insufficiency due to lower nephron nephrosis, *New England Jr. Med.*, 1948, ccxxxix, 693-700.
98. TOMB, J. W.: Anuria and anoxia, *Jr. Trop. Med.*, 1942, xlv, 125.
99. TOMB, J. W.: Crush injury and anoxia, *New Zealand Med. Jr.*, 1943, xlii, 75-77.
100. TRUETA, JOSEPH, BARCLAY, A. E., DANIEL, P. M., FRANKLIN, K. J., and PRICHARD, MARJORIE M. L.: Studies of the renal circulation, 1947, Blackwell Scientific Publications, Oxford.
101. VANDER VEER, J. B., and FARLEY, D. L.: Mushroom poisoning (mycetismus); report of 4 cases, *Arch. Int. Med.*, 1935, lv, 773-791.
102. VAN SLYKE, D. D.: The effects of shock on the kidney, *Ann. Int. Med.*, 1948, xxviii, 701-722.
103. VAN SLYKE, D. D., PHILLIPS, R. A., HAMILTON, P. B., ARCHIBALD, R. M., DOLE, V. P., and EMERSON, K., JR.: Effect of shock on kidney, *Trans. Assoc. Am. Phys.*, 1944, lviii, 119-127.
104. VERMOOTEN, VINCENT, and HARE, D. M.: The use of continuous gastric lavage in the treatment of uremia associated with prostatism, *Jr. Urol.*, 1948, lix, 907-919.
105. WAKEMAN, A. M., MORRELL, CLARE A., EISENMAN, ANNA J., SPRUNT, D. L., and PETERS, J. P.: Metabolism and treatment of blackwater fever, *Am. Jr. Trop. Med.*, 1932, xii, 407-439.
106. WEAR, J. B., SISK, I. R., and TRINKLE, A. J.: Peritoneal lavage in treatment of uremia: experimental and clinical study, *Jr. Urol.*, 1938, xxxix, 53-62.
107. WINSOR, TRAVIS, and BURCH, G. E.: Renal complications following sulfathiazole therapy, *Jr. Am. Med. Assoc.*, 1942, cxviii, 1346-1353.
108. YORKE, WARRINGTON, and NAUSS, R. W.: The mechanism of the production of suppression of urine in blackwater fever, *Ann. Trop. Med.*, 1911-1912, v, 287-312.
109. YOUNG, J.: Renal failure after utero-placental damage, *Brit. Med. Jr.*, 1942, ii, 715-718.
110. YUILE, C. L.: Hemoglobinuria, *Physiol. Rev.*, 1942, xxii, 19-31.
111. YUILE, C. L., and CLARK, W. F.: Myohemoglobinuria; study of renal clearance of myohemoglobin in dogs, *Jr. Exper. Med.*, 1941, lxxiv, 187-196.
112. YUILE, C. L., GOLD, M. A., and HINDS, E. G.: Hemoglobin precipitation in renal tubules; a study of its causes and effects, *Jr. Exper. Med.*, 1945, lxxxii, 361-374.

# NECROSIS OF RENAL PAPILLAE\*

By EDWARD D. ROBBINS, M.D., *Chicago, Illinois*, and ALFRED ANGRIST, M.D., *Long Island, New York*

## INTRODUCTION

NECROSIS of the renal papillae is a curious and striking lesion which most pathologists meet only occasionally at the autopsy table. The purpose of this presentation is to report briefly the cases of this disease seen at the Queens General Hospital, to discuss some of the theories of its pathogenesis, and more particularly, to relate this lesion to a similar one produced in the experimental animal by a dietary deficiency of certain fatty acids.

*Necrosis of Renal Papillae in Man.* The literature concerning this lesion, which is variously known as renal papillitis, medullary necrosis, papillitis necroticans, necrotizing renal papillitis, etc. has recently been reviewed in detail by Edmondson, Martin, and Evans.<sup>1</sup> These authors have traced the first case report back to 1877, but Günther<sup>2</sup> in 1937 first emphasized the frequent association of diabetes with this lesion.

Approximately 110 cases were reported in the literature up to 1947,<sup>1, 4, 5</sup> and of these, 62 had diabetes and 48 did not; of the latter, 85 per cent had urinary tract obstruction. From the large series reported by Edmondson et al.<sup>1</sup> and by Robbins, S. L., Mallory and Kinney,<sup>5</sup> it is apparent that 12 to 20 per cent of diabetics coming to autopsy have acute pyelonephritis. Of these, 25 per cent have necrosis of the papillae. Hence the lesion may be found in 3.2 to 5 per cent of all diabetics. In contrast, 3.3 per cent of non-diabetics coming to autopsy have acute pyelonephritis. Of these, 2 per cent have necrosis of the papillae. Hence the lesion may be found in only 0.06 per cent of non-diabetics. The overall incidence of the disease in pyelonephritis is about 4 per cent.<sup>1</sup> Robbins, Mallory and Kinney found that in 74 per cent of their cases, death was attributable directly to the papillary necrosis.

The great majority of non-diabetics who have papillary necrosis have some obstruction of the urinary tract. This was present in six out of seven cases in one series,<sup>5</sup> in 20 out of 21 cases<sup>1</sup> in another; and in five out of six of our cases. Benign hypertrophy of the prostate is the usual cause, but carcinoma of the prostate, urethral stricture, "cord" bladder and renal calculi have also been found.

The variation in sex incidence is also striking. In diabetics, the ratio of females to males is 2:1; in non-diabetics the ratio of females to males is 1:6, due to greater frequency of urinary tract obstruction in males, chiefly

\* Received for publication October 14, 1948.

The Transactions of the New York Pathological Society contain an abstract of this paper, together with discussion.

from the prostate. The clinical picture of this disease may be acute or subacute. The acute cases are usually diabetics who have a short history of illness, often with a sudden onset, with a rapidly fatal course over a period of a few days. They are often seen in coma, with or without acidosis, and usually have azotemia. There is pyuria, often hematuria, a high fever and often leukocytosis. The subacute cases, usually, are: (1) diabetics with pyelonephritis that have been followed for a period of days or weeks, who suddenly became worse; (2) diabetics who develop a septicemia secondary to some focus of infection, e.g., a carbuncle, and are found to have pyuria and azotemia,<sup>1</sup> (3) non-diabetics, usually with chronic obstruction of the urinary tract, who develop a severe urinary tract infection, with sepsis and azotemia. The course of the latter group is difficult to differentiate from suppurative pyelonephritis without papillary necrosis.

Occasionally the sloughing of a papilla will result in renal colic, and/or hematuria, with a defect of the calyces on pyelography, which may suggest renal stone, tumor, or tuberculosis.<sup>2</sup> Alken<sup>3</sup> described a case of a female diabetic with pyuria and hematuria, with defects in some calyces on pyelography. Six months later a sloughed papilla was passed, and pyelography demonstrated defects in all the calyces.

The kidneys are usually enlarged and heavier than normal. The cortex is usually studded with abscesses. The papillary necrosis is bilateral in the majority of diabetics, but more often unilateral in the majority of non-diabetics. The degree of necrosis of the renal papilla varies. It may be (1) confined to the tip of the papilla, (2) confined to a small central portion of the papilla, (3) involve most of the papilla, (4) involve all of the papilla and part of the pyramid (extending in rare cases up to the corticomedullary junction), (5) the necrotic papilla may show a separation at the line of demarcation from the rest of the pyramid, (6) the papilla may be sloughed out entirely. The renal columns of Bertini are never involved, nor does the lesion ever extend to involve the cortex. The necrotic papillae are brownish, or yellowish-green in color and are sharply demarcated from the rest of the kidney.

Microscopically there is an acute pyelonephritis with or without supuration in the cortex and medulla. The affected papillae show a pale staining, infarct-like necrosis of all elements—tubules and interstitial tissue, with shadow-form preservation of the general architecture. In the collecting tubules, there may be found bluish masses of cocci or rod-shaped bacteria; but in the necrotic papilla there are no interstitial abscesses or diffuse inflammatory infiltrate. At the line of demarcation, there is a zone of infiltration of polymorphonuclears and round cells, along a narrow line of necrotic tissue, and above this, marked vascular congestion. An acute pyelitis of varying severity is present.

*Necrosis of Renal Papillae in a Deficiency Disease of Rats.* In 1929 Burr and Burr<sup>7</sup> described a new deficiency disease in rats fed a diet which

was virtually fat-free. This diet consisted of sucrose, casein which was carefully purified and rendered fat free by ether extraction, McCallum's salt mixture, ether extracted yeast for the vitamin B complex, the non-saponifiable matter from cod liver oil for vitamins A and D, and in later experiments the non-saponifiable matter from wheat germ oil for vitamin E.

Rats fed such a diet from the day of weaning develop (1) a lesion of the tail characterized by scaliness, inflammation, swelling, and later necrosis of the tip, (2) redness, swelling and scaliness of the feet, (3) dandruff and loss of body hair, (4) cessation of growth, (5) bloody urine. The animals maintained a plateau of the weight curve for weeks and months, then declined in weight and died. At autopsy, five of the eight animals had abnormal kidneys. It was felt that the immediate cause of death was kidney degeneration.

The addition of 10 drops of lard daily to the diet of these diseased animals produced a prompt cure of all lesions and a gain in weight; while the addition of 2 per cent of the total diet as lard from the beginning of the experiment completely protected the animal from the disease. Furthermore, the addition of pure glycerol, or the non-saponifiable matter from lard did not protect against the disease, but 13 drops of the fatty acid fraction from lard did give protection. Feeding 200 mg. per day of the fatty acid fraction of lard to a diseased rat on the fat free diet produced a 2 gram/day increase in weight, a tenfold effect.

They demonstrated by a series of experiments that (1) the disease is not due to a deficiency of vitamins A, B, D or E; (2) the fat free yeast, and the non-saponifiable matter from cod liver oil, and from wheat germ oil, were adequate sources of these vitamins and that (3) these latter substances were absorbed in the absence of fat in the diet. By feeding oils of various composition with regard to saturated and unsaturated fatty acids, it was shown that cures could only be effected by unsaturated fatty acids, and of these, only linoleic or acids of higher unsaturation. Oleic acid, and saturated fatty acids were without effect. The authors concluded that warm blooded animals cannot synthesize appreciable quantities of linoleic acid, or more unsaturated fatty acids.

Later experiments<sup>8</sup> demonstrated that (1) the respiratory quotient of rats with the fat deficiency disease rises above unity after carbohydrate feeding, indicating the formation of fat from carbohydrate, but the persistence of the disease proves that linoleic or other more unsaturated fatty acids are not formed.<sup>9</sup> (2) The highly unsaturated fatty acids of cod liver oil can be used by fat deficient rats for growth, but the skin lesions can only be cured by linoleic or linolenic acids, which are lacking in cod liver oil.<sup>10</sup> (3) Feeding pure fatty acids as the methyl esters proves again the complete ineffectiveness of oleic acid, the curative value of linoleic and linolenic acids, and the ineffectiveness of alpha eleostearic acid, an isomer of linolenic acid.<sup>11</sup> (4) The scaly skin and tail necrosis in this disease are not a symptom com-

plex unique to fat deficiency but are found in other deficiency states as in malnutrition, avitaminosis B, avitaminosis G, diets containing rancid fat, and those rich in egg white. However, these changes, plus growth arrest and kidney degeneration (in the presence of adequate quantities of water soluble growth factors, together with vitamins A, D, and E), which are readily cured by an adequate fat, constitute a specific disease complex.<sup>12</sup> (5) The iodine number of serum fatty acids of rats on fat free diet indicates that these fatty acids are less unsaturated than controls.<sup>13, 14</sup> (6) Metabolism studies on fat deficient rats indicate that the basal metabolic rate is higher, the respiratory quotient higher, and the specific dynamic action of foods is higher, and that these rats synthesize large amounts of fat but this does not prevent their fat deficiency syndrome.<sup>15</sup> (7) Feeding pure fatty acids to fat deficient rats discloses certain differences in the effects produced by linoleic, linolenic and arachidonic acids, and hence they must be treated individually in nutrition studies.<sup>16</sup>

In 1931, Borland and Jackson<sup>17</sup> reported the pathology of the kidneys of rats fed on the fat free diet of Burr and Burr. The results were as follows: A group of 21 rats with the fat deficiency disease were autopsied. The kidneys were large and pale, with an average weight of 21 per cent over the Wistar norm. Some were coarsely granular. In eight of the 21 animals, the papillae appeared largely necrotic and much of certain papillae might be sloughed off into the pelvis. In these, irregular masses of the necrotic material stained a deep blue with hematoxylin and black with von Kossa's stain, demonstrating calcium.

Microscopy revealed no changes in the glomeruli. Certain cortical tubules showed cells which stained deep blue with hematoxylin, and black with von Kossa's stain, indicating the deposition of calcium. The lumina of these tubules often contained debris which was also calcified. These changes were present in 15 of the 21 cases. There was no inflammatory infiltrate noted. Widespread degenerative changes in cortical tubules (sloughing of cytoplasm, pyknosis, etc.) occurred in eight cases. Sudan III stains showed increase in intracellular fat or lipid in 18 cases. Occasionally there was dilatation of some of the cortical tubules, suggesting obstruction to the flow of urine in the papillary ducts. In the medulla, degenerative changes were found in cells of the papillary ducts. Sudan III stains showed fine fat or lipid droplets in these cells and adjacent interstitial tissue. Fatty casts and casts of a homogenous blue-staining substance were often present. Higher up in the pyramid, casts of fatty albuminous material appeared in degenerating ducts, and, as the necrotic area was approached, this material as well as the degenerating tissue became intermingled with deposits of calcium. In two of these eight cases, bacteria and a few polymorphonuclear leukocytes were present in the necrotic area, but in the remaining kidneys no inflammation was found.

In 10 cases, proliferation of the pelvic epithelium occurred, but no keratosis such as is found in avitaminosis A was present. In a group of rats

with fat deficiency disease, in which cures were attempted with various inadequate fats, the same changes were noted as above. However, calcification of the papilla and apical necrosis were present in one rat of nine. In a group of rats in whom the deficiency disease was first induced, and then cured by the addition of lard to the diet, the kidneys were normal grossly and microscopically. Another group of 35 rats with the fat deficiency disease was treated with various fats including linseed oil, corn oil, olive oil, etc. At autopsy, the general condition was fair to good, the animals being only 10 per cent underweight on an average. However, degenerative changes and calcification of cortical tubule cells were widespread. Degeneration of papillary ducts was found in 21 cases, with calcification and necrosis of the papillae in seven of the 21. The necrotic areas were smaller than those found in the first group.

Thirty-eight rats, which were fed diets containing lard, or a regular stock diet, were used as the controls.

These authors concluded that characteristic renal lesions were present in rats fed on a diet free of fat but otherwise adequate. The most striking lesion was calcification of tubules and necrotic areas in the renal medulla, with disintegration of the apex of the pyramid in some. The addition of lard to the diet prevented the renal lesion, or cured it to a large extent.

### MATERIAL

Fourteen cases of papillary necrosis which were autopsied at the Queens General Hospital, are described below. These include 13 acute cases, and one which was healed. Eight of these cases were diabetics and six non-diabetics.

### DIABETIC CASES

Seven acute cases, and one with healed papillitis were found in diabetics. (The latter will be discussed separately.) There were six females, and two males, in an age range from 42 to 79 years, with an average age of 57. Two patients were admitted to the hospital in coma, and one was stuporous. Three patients died in 18 hours or less after entering the hospital. Two of these had 3 to 4 plus glycosuria, but no acetone; yet both were thought to be in diabetic coma. The shortest total duration of illness from the first symptoms was 3.5 days. The urine was abnormal in all the acute cases, though only three were noted to have pyuria. In the three acute cases in which blood urea levels were done, all had marked azotemia. In the four cases in which the hemoglobin was reported, it varied from 8.5 to 10.5 grams, with red cell counts between 3 and 3.5 million. Three had unilateral papillary necrosis, and two showed unilateral pyelonephritis.

The single male patient in the acute cases had benign prostatic hypertrophy with urinary retention and a cystotomy was performed during his hospital course.



## CASE REPORTS

*Case 1.* This 42 year old white female was admitted to the hospital in coma. She was known to have had diabetes for 12 years. For the past week, she had been semi-comatose.

Physical examination revealed an emaciated woman in deep coma, with twitching of the facial muscles, and a uremic frost on the skin. Blood pressure 118 mm. Hg



FIG. 1. Kidney of a diabetic patient showing extensive supplicative pyelonephritis with sharply limited zones of necrosis in the pyramids. Note the narrow hyperemic and exudative marginal reactive zones.

systolic and 58 mm. diastolic; temperature 101.2°; respirations rapid. Laboratory data: Urine: grossly bloody; sugar 3 plus; acetone 0; albumin 3 plus; many casts.

The patient made no response to treatment (insulin and infusions) and died 18 hours after admission.

Clinical diagnosis: Uremia; diabetic coma; malnutrition and avitaminosis.

At autopsy, the kidneys contained multiple cortical abscesses, with a perirenal abscess on the left. Necrosis of the papillae was present in the left kidney. The pelves and ureters were dilated and revealed ecchymoses. There was a bullous hemorrhagic cystitis. Microscopy revealed advanced papillary necrosis (figures 1 and 2).

*Case 2.* This 57 year old Negro female was admitted in coma. The past history was not known, but she was reported to have been "sick" for eight days. On physi-



FIG. 2. Micro-photograph showing junction zones between necrotic tissue of papilla and viable tissue with inflammatory reaction in between.

cal examination, she was in deep coma, dehydrated, hyperpneic, and had an acetone odor on the breath. Temperature 102°.

Laboratory data: Urine: milky; glucose 4 plus, acetone 3 plus; loaded with pus cells and pus casts. Six hours later, after she had received 725 units of insulin, three liters of Hartman's solution, and intravenous sulfadiazine, the glycosuria fell to 1 plus, the acetonuria disappeared, and she showed signs of returning consciousness. She

died suddenly, 11 hours after admission. An ante-mortem blood culture grew *B. coli*.

Clinical diagnosis: diabetic coma; pyelonephritis; *B. coli* septicemia.

At autopsy, the right kidney contained many cortical and medullary abscesses. The right ureter was dilated and had a thickened wall. The left kidney and ureter were unremarkable. The bladder had a hemorrhagic mucosa. Papillary necrosis was found and very marked on microscopic section.

*Case 3.* A 49 year old white female was admitted with a three day history of abdominal pain, nausea and vomiting. She was known to have diabetes for 12 years. She had not eaten nor taken insulin for the past three days.

Physical examination revealed an obese patient, with temperature 99.6°, and blood pressure 114 mm. Hg systolic and 76 mm. diastolic. The heart was not enlarged. The knee jerks and ankle jerks were absent.

Laboratory data: Initial urine: albumin, trace; glucose 4 plus; acetone 0; microscopically negative. Blood urea 52 mg. per cent, creatinine 3 mg. per cent, sugar 400 mg. per cent. White blood cells 7500, 83 per cent polys, later 19,100; Hb. 8.5 gm.

Four days after admission the patient suddenly went into shock, with pale, clammy skin, low blood pressure, and cyanosis. Complete heart block was noted. She died on the seventh hospital day.

Clinical diagnosis: Arteriosclerotic heart disease with myocardial infarction; diabetes mellitus with neuropathy.

At autopsy, the left kidney contained many cortical abscesses, and areas of "pallor" in the pyramids. The left pelvis and ureter were dilated and hemorrhagic. The right kidney, pelvis, and ureter were unremarkable. The bladder mucosa was thickened and red about the left ureteral orifice. The microscopic examination revealed advanced papillary necrosis.

*Case 4.* This 63 year old white male entered the hospital with a four year history of urinary frequency, nocturia, urgency and dribbling. For the past three days he had been vomiting and complained of an acid taste in the mouth. He was known to have diabetes for many years but was controlled without insulin.

Physical examination revealed 2 plus enlargement of the prostate which was soft and not fixed. Blood pressure 150 mm. Hg systolic and 80 mm. diastolic. He had uncontrollable hiccoughing.

Laboratory data: Urine: glucose 4 plus; 15 white cells per high power field. White blood cells 16,200; 87 per cent polynuclears; Hb. 8.5; red blood cells 3.4 million. Blood urea 65 mg. per cent; blood sugar 416 mg. per cent.

He was given insulin, penicillin, sulfa drug and infusion. The blood urea returned to normal in 11 days. The blood sugar dropped to 250 mg. He began to run an irregular fever up to 102°. A cystotomy was performed. The urea then rose to 41. CO<sub>2</sub> combining power was reported as 41 vol. per cent.

Bladder culture grew *Streptococcus hemolyticus* and *B. proteus*. He grew weaker, developed bed sores, and died on the twenty-eighth hospital day.

Clinical diagnosis: Pyelonephritis; diabetes mellitus.

At autopsy, the kidneys contained multiple cortical abscesses, the pelvis were dilated and had red granular mucosa. There was an acute ureteritis and cystitis. Microscopic sections disclosed circumscribed areas of shadow necrosis within the papillae.

*Case 5.* This 73 year old, white female entered the hospital because of a sore on the big toe which had been present for several months. She was known to have had diabetes for six years.

Physical examination: There was gangrene of the big toe. Blood pressure 130 mm. Hg systolic and 76 mm. diastolic.

Laboratory data: Urine: Albumin 3 plus; glucose 2 plus; microscopically negative; Hb. 9.5 gm.; red blood cells 3.29 millions; white blood cells 7650. Blood sugar 315 mg. per cent.

She developed an abscess of the buttock, which was incised and drained. She ran a spiking temperature, deteriorated rapidly, and died on the eleventh post operative day (the fifty-first hospital day).

Clinical diagnosis: Diabetes mellitus; arteriosclerotic heart disease; abscess of buttocks; bronchopneumonia.

At autopsy, the kidneys were large, pale, and contained many cortical abscesses. There was bilateral renal papillitis, bilateral ureteritis, and cystitis. Microscopy showed circumscribed areas of typical necrosis of the renal papillae.

Case 6. This 43 year old, white female had fractured the right hip 10 weeks previously. After three weeks at another hospital, she was sent home where she began to vomit continuously for the next two weeks. For the past 12 days the urine had been bloody, and there had been a bloody stool on the day of admission. The past history included treatment for lues and known diabetes for 14 years.

Physical examination revealed a stuporous pale patient, with Argyll-Robertson pupils, absent knee and ankle jerks; and blood pressure 80 mm. Hg systolic and 60 mm. diastolic.

Laboratory data: Urine—albumin 2+, glucose 0, acetone 0, micro-clumps of pus cells and many red blood cells. Hemoglobin 8 gm., white blood cells 15,200 with 88 per cent polynuclears. Blood urea 170 mg. per cent. Blood sugar 140 mg. per cent.

Cystoscopy revealed a necrotizing cystitis with involvement of the trigone. The blood urea fell to 85 mg. per cent but CO<sub>2</sub> combining power was found to be 33 vol. per cent. Culture of the bladder: *B. coli* and *Streptococcus non-hemolyticus*. The white blood count rose to 30,700 with 89 per cent polynuclears. The urines were maintained sugar free. She died on the tenth hospital day.

Clinical Diagnosis: Diabetes mellitus; necrotizing cystitis; acute pyelonephritis.

At autopsy the kidneys were large and smooth. All the renal papillae showed yellowish necrosis. There was an acute ureteritis and a severe hemorrhagic cystitis. Microscopy revealed an advanced papillary necrosis.

Case 7. This 52 year old white female was admitted with a six hour history of aphasia and weakness of the legs. She had complained of being "sick" for the previous three days but the nature of her complaints was not known. She had complained of headaches, dizziness and nocturia for the past year.

Physical examination revealed an obese, aphasic patient with a temperature of 99.2°. There was no paralysis of the extremities, but the left naso-labial fold was flattened. The plantar reflexes were normal.

Laboratory data: Urine—glucose 4 plus, acetone 0, no casts, microscopically negative.

Her temperature rose rapidly to 105.4°. She died 17 hours after admission.

Clinical diagnosis: Cerebrovascular accident; diabetes mellitus.

At autopsy the papillae of both kidneys were necrotic. The pelves were injected; the ureters and bladder were unremarkable. There were no areas of hemorrhage or softening in the brain. On microscopy the necrosis of the papillae was advanced.

Case 8. This 79 year old white male was admitted from a convalescent home. One month previously his right leg had been amputated for gangrene. He was a known diabetic, regulated by diet alone. On admission he was pale and disoriented. The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. The heart was enlarged. Basal râles were present in both lungs. The prostate was 3 plus enlarged, hard, nodular and non-tender. There was a right mid-thigh amputation stump.

Laboratory data: Urine—albumin 0, sugar 0, white blood cells 8000, hemoglobin 8 gm. Blood urea 17 mg. per cent, blood sugar 98 mg. per cent. A chest roentgen-ray was reported as negative.

He was treated with mercupurin and digitalis. A low grade fever appeared. Death occurred on the eleventh hospital day.

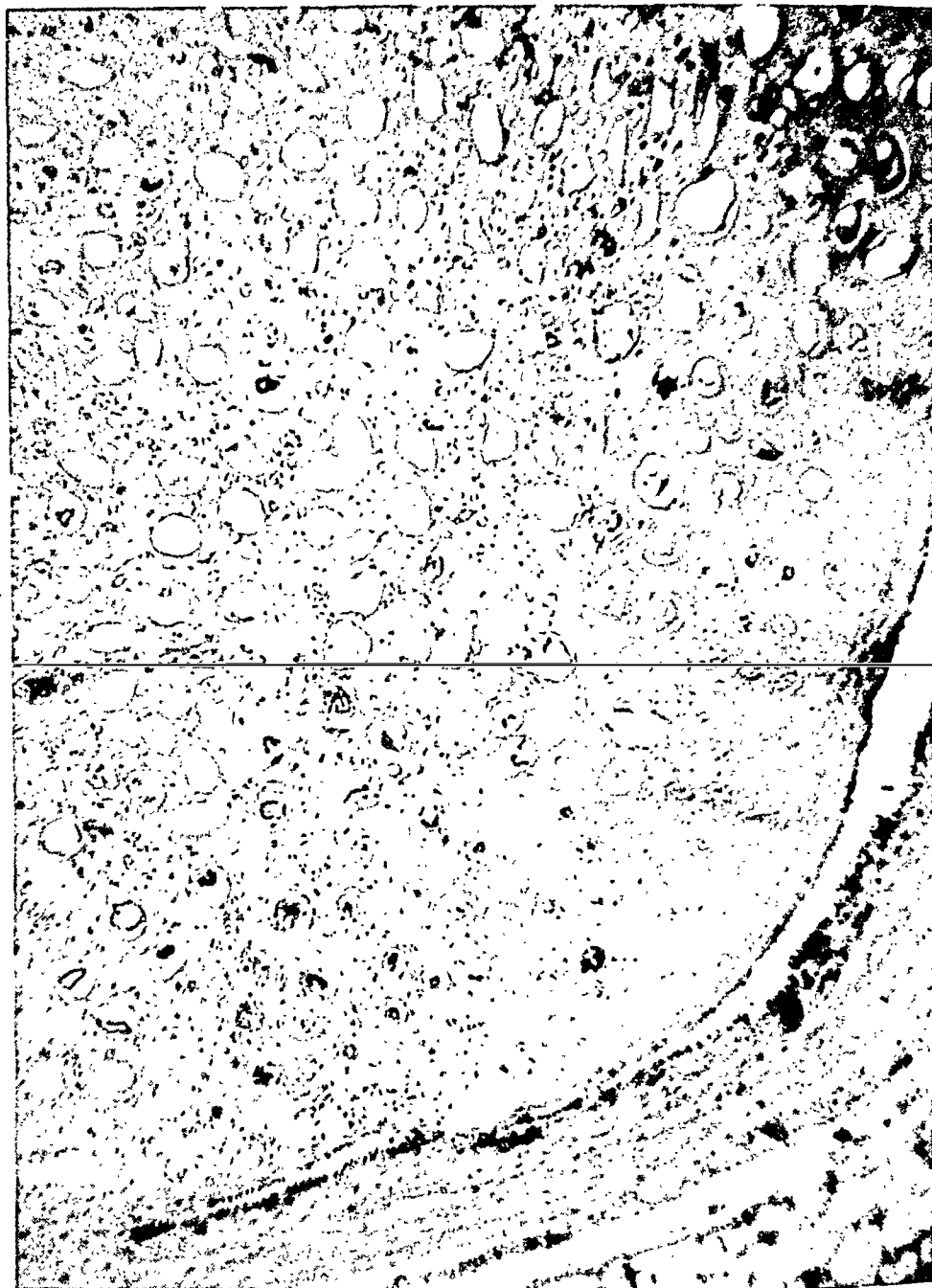


FIG. 3. Tip of pyramid in the stage of healing of papillary necrosis showing epithelization after absorption of necrotic material.

Clinical diagnosis: Hypertensive and arteriosclerotic heart disease III C; diabetes mellitus; anemia.

At autopsy the left kidney was unremarkable except for a 2 cm. cortical adenoma. The right kidney was unremarkable except for the papillae, which were atrophic and fibrotic. The pelvis was not dilated. The ureters were patent. The bladder showed moderate trabeculation, but no evidence of inflammation. Microscopy revealed healed renal papillitis of the right kidney (figure 3).



FIG. 4. Note hydronephrosis resulting from absorption of necrotic papillae in the upper-most and lower-most calyces.

Case 8 with healed papillary necrosis, deserves special mention. He was an elderly diabetic who had had an amputation of the right leg one month before admission. The urine was negative and the blood urea nitrogen was not elevated. He died on the eleventh hospital day of a severe broncho-

pneumonia. At autopsy, the right kidney revealed atrophic and fibrotic stumps of papillae. On microscopy the papillae showed a deformed and shortened tip, covered by pelvic epithelium. Many of the collecting tubules near the tip of the papillae were simply empty holes in a hyalin interstitial matrix, but others had an epithelial lining which seemed to be growing downward from the region of the base of the pyramid into the distal collecting tubules.



FIG. 5. Necrotic papillae undergoing resorption. Note the delimited zone of hyperemia at the junction of cortex and medulla suggesting a significant vasomotor component in this pathological process.

It seems evident that such healed absorbed papillae finally give rise to dilatation of the corresponding region of the pelvis of the kidney. Recurrent milder lesions of this type or a single attack of massive necrosis of the inner medulla with final resorption and epithelization offers one demonstrable mechanism for the development of hydronephrosis, particularly obstructive hydronephrosis (figures 4 and 5).

#### NON-DIABETIC CASES

The five male non-diabetics form a strikingly homogeneous group. They were all over 73 years of age, with an average age of 77. Their illness began a month or more before admission in four cases out of five. The hospital stay was prolonged, ranging from 26 days to 3.5 months, averaging about two months. They all had chronic lower urinary tract obstruction (three

benign hypertrophy and two carcinomas of the prostate). Four of the five had prostatic operations during their hospital stay. All had azotemia. All were moderately anemic, with hemoglobins ranging from 8.5 to 11 grams, and red cell counts from 3 to 4 million. Pyuria was found in four cases, and hematuria in four cases (two gross, two microscopic).

At autopsy all had extensive upper and lower urinary tract inflammatory disease, with cystitis, ureteritis and bilateral pyelonephritis. Only two of the six had advanced necrosis of the papillae—the others revealed limited areas of necrosis within the papillae in areas of acute pyelonephritis.

The lone female had striking bilateral advanced papillary necrosis, but only a moderate urinary tract infection. She had, in addition, a fractured skull, portal cirrhosis and jaundice. The urine was reported sugar free, but a blood sugar was found to be 186 mg. per cent so that this case may well belong to the diabetic group.

#### CASE REPORTS

*Case 1.* This 73 year old female fell at home and struck her head. One week later she developed nose bleeds, and jaundice, and was admitted to the hospital. The skin and sclerae were icteric. The liver was palpable one finger's-breadth below the costal margin. Roentgenograms of the skull revealed a fracture in the mastoid region probably extending to the base.

Laboratory data: Urine: albumin 2+, glucose 0, 12 red blood cells per high power field, and 10 white blood cells per high power field. There were no clumps or casts. Hemoglobin 10.5 gm.; red blood cells 3.4 millions; white blood cells 31,100 with 87 per cent polynuclears. Non-protein nitrogen 162 mg. per cent. Blood sugar 186 mg. per cent.

She became comatose, incontinent, and developed projectile vomiting and tarry stools. Her temperature varied from 99° to 101°. She died on the seventh hospital day.

At autopsy the kidneys revealed advanced bilateral papillary necrosis. The microscopic sections demonstrated the classical histology of advanced papillary necrosis (figure 6).

*Case 2.* This 74 year old white male entered the hospital because of difficulty in urinating during the preceding month. Two weeks before admission he had complete retention and was catheterized on several occasions. On rectal examination, the prostate was enlarged (grade 2), but not hard.

Laboratory data: Urine on admission—albumin 2 plus, glucose 0, microscopically negative. Later specimens were grossly bloody, and contained pus cells. Hemoglobin 8.5 gm., red blood cells 3.1 millions. The blood urea was 15 mg. per cent.

A one stage perineal prostatectomy was performed. Three weeks after operation, necrosis of the anterior rectal wall and the operative site occurred. His condition deteriorated, the blood urea rose to 50 mg. per cent, and he died on the fiftieth hospital day.

Clinical diagnosis: Post-operative perineal prostatectomy with necrosis of anterior rectal wall, sepsis and anemia; arteriosclerotic heart disease.

At autopsy there was a marked bilateral suppurative pyelonephritis, an acute ureteritis, and a hemorrhagic cystitis. On microscopic section the renal papillae showed small circumscribed areas of necrosis of characteristic form.

*Case 3.* A 78 year old white male entered the hospital with complaints of difficulty in urinating (frequency, nocturia, dysuria) for one month. Rectal examination revealed a fixed, irregular, hard prostate. Temperature 100.2°.



Laboratory data: Urine—albumin 4 plus, glucose 0, acetone 0; microscopic showed red and white blood cells too numerous to count. White blood cells 42,000 with 45 per cent polynuclears. Hemoglobin 62 per cent, red blood cells 3.47 millions. The blood urea was 48 mg. per cent. He ran an irregular fever up to 102.8°. The blood urea rose to 108 mg. per cent. The patient died on the twenty-sixth hospital day.

Clinical diagnosis: Carcinoma of the prostate; uremia

At autopsy the renal papillae were necrotic. Some were detached and lying free in the pelvis. The pelvis was filled with pus. There was acute necrotizing ureteritis and cystitis. Microscopic sections demonstrated advanced papillary necrosis.

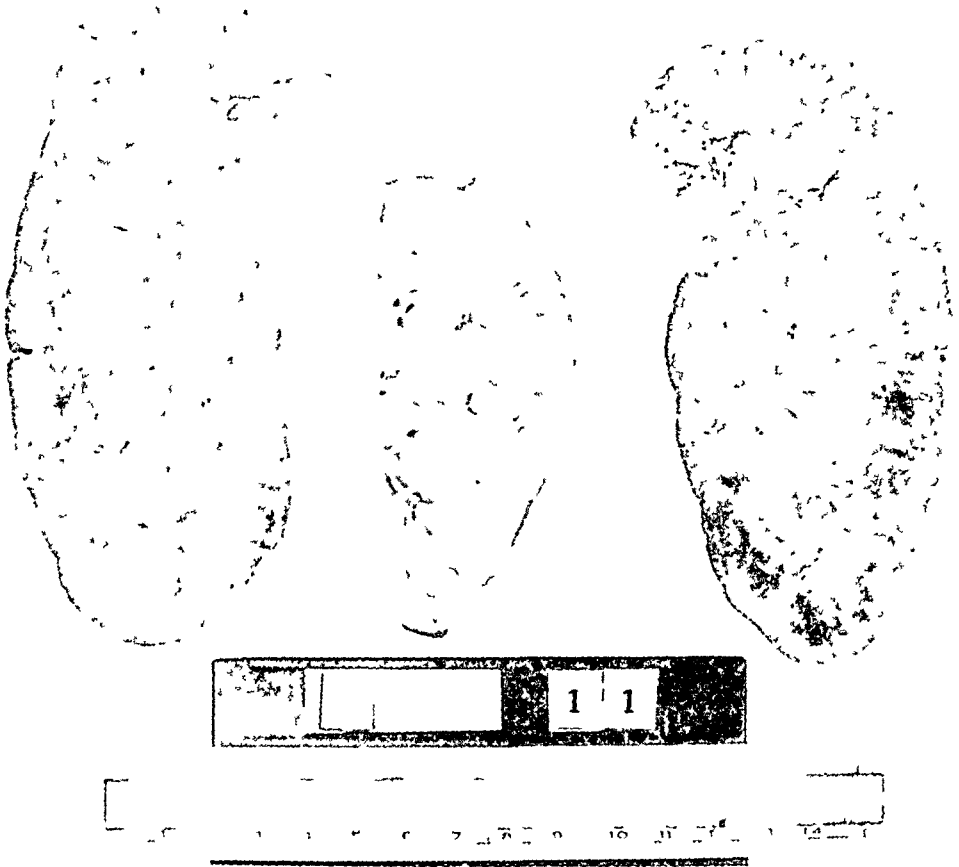


FIG. 6 Section of the kidney of a non-diabetic patient showing gross necrosis of the papillae. Note the sharp limitation of the whitish necrotic zones

*Case 4.* This 78 year old white male entered the hospital complaining of inability to void, for the past three days. He had been catheterized once in that interval. There was a three year history of nocturia. Rectal examination revealed 2 plus enlargement of the prostate, which was soft, and not fixed.

Laboratory data: Urine—albumin 4 +, glucose 0 and many red cells with occasional white blood cells. Hemoglobin 7 grams, red blood cells 3.1 million. The white blood cell count rose from 5,000 to 18,000. Blood urea 24 mg. per cent

A two stage suprapubic prostatectomy was performed, following which he ran a stormy course, with breakdown of the operative wound. He died three and one-half months after admission.

Clinical diagnosis: Benign prostatic hypertrophy; uremia.

At autopsy, bilateral suppurative pyelonephritis, with ureteritis and gangrenous cystitis, was disclosed. Microscopy revealed small areas of non-reactive central necrosis within the papillae.

*Case 5.* This 77 year old white male entered the hospital with the history of progressive swelling of both legs, which spread to involve the scrotum and abdomen. Dyspnea and orthopnea had been present for the preceding nine months. He had frequency and nocturia. There was no history of diabetes.

Physical examination: Blood pressure 130 mm. Hg systolic and 80 mm. diastolic. The heart was not enlarged, but was fibrillating. Ascites was present. The liver was palpable two fingers below the costal margin. There was 4 plus pitting sacral and leg edema.

Laboratory data: Urine—albumin 0, glucose 0, 40 red blood cells per high power field. Blood urea 29 mg. per cent, blood sugar 125 mg. per cent.

He developed urinary retention which required an indwelling catheter. A spiking fever developed. He was given sulfa drug in small doses. On the nineteenth hospital day sulfa crystalluria with many white blood cells and red blood cells was found. The blood urea rose to 31 mg. per cent. A cystotomy was performed. His condition improved, and he became ambulatory. The blood urea on the thirty-sixth hospital day was 17 mg. per cent. A trans-urethral resection was performed. Following this he developed a shaking chill. Plasma (200 c.c.) was given. The next day he was jaundiced. The blood urea rapidly rose to 65 mg. per cent and then to 124 mg. per cent with 13.6 mg. per cent creatinine. The icteric index was 50. He died on the forty-fifth hospital day.

At autopsy, the kidneys contained multiple abscesses in the cortex. Microscopic sections revealed small areas of necrosis within the papillae, with only marginal reaction.

*Case 6.* This 81 year old white male was admitted to the hospital because of urinary retention with overflow incontinence. He had had symptoms of prostatism for five years, which had become markedly aggravated within the previous two months (frequency, nocturia, weak stream, etc.).

Physical examination: The bladder was palpated up to the umbilicus. The prostate was 1 plus enlarged, but soft.

Laboratory data: First urine—grossly bloody, albumin 2 plus, glucose 0, blood urea 17 mg. per cent.

A two stage suprapubic prostatectomy was performed. He ran a febrile course. The urine continued to show 2 plus albumin, and white cells. Blood urea rose to 34 mg. per cent. He died on the fifty-second hospital day.

Clinical diagnosis: Benign hypertrophy of prostate; hydronephrosis; pyelonephritis.

Autopsy disclosed multiple cortical abscesses in the kidneys. Papillary necrosis was noted bilaterally. The microscopic sections revealed small areas of necrosis within the pyramids.

### THEORIES OF PATHOGENESIS

A variety of theoretical explanations of the pathogenesis of necrosis of the renal papilla has been advanced.

*I. The Rôle of Infection.* It is at once apparent that all of the cases occur in association with active pyelonephritis, which is usually suppurative. The toxins of bacteria,<sup>2</sup> the coagulase and necrosin of *Staphylococcus aureus*,<sup>1</sup> and the toxic metabolic products of *B. coli*<sup>18</sup> have all been suggested as factors in the production of the lesion. However, the multiplicity of the bac-

terial flora which is found makes it appear certain that papillary necrosis is unrelated to any specific bacterium.<sup>6</sup> Since no similar necrosis is found in the renal cortex, it is clear that bacterial toxins alone cannot account for the lesion. The bacterial colonies found in the tubules of the necrotic papilla are not simply the result of postmortem proliferation, for Günther<sup>2</sup> found them in surgically removed kidneys as well as in autopsy specimens.

*II. The Rôle of Circulation.* The blood supply to the pyramid and papilla is poor compared to that of the cortex, being composed of small afferent arterial capillaries and efferent venules lying between the excretory tubules. The infarct-like necrosis which is the chief characteristic of renal papillitis at once suggests vascular occlusion. However, there is no single vessel which could produce such an infarct, and hence the presence of multiple capillary thromboses might be assumed. These are by no means constantly present, or very marked when found; Edmondson et al.<sup>1</sup> noted thrombosis of capillaries in a few kidneys, and extensive thrombophlebitis of the venous system in five kidneys. Davson and Langley<sup>18</sup> found no vascular occlusion. Robbins, S. L., et al.<sup>5</sup> found scattered capillaries containing fibrin thrombi at the base of the pyramid. We have been impressed by the paucity of thrombi in our material. Sheehan<sup>19</sup> suggested the possibility of spasm or acute degeneration of the walls of medullary vessels, such as is seen in cortical necrosis, but the cortical lesion has not been described in cases of papillary necrosis.

The remarkable studies of the renal circulation by Trueta and his colleagues<sup>25</sup> throw new light on many forms of renal disease, and force a re-examination of many old concepts of renal physiology. It is apparent from their work that the kidney has two potential circulations, one through the cortical glomeruli, and one through the juxtamedullary glomeruli and the vasa recta of the medulla. It was found that under certain conditions, blood may pass almost exclusively through one or the other of these renal circuits, thus by-passing the second circuit. The usual circumstance was a by-passing of the cortex via the medullary circuit. In this manner the authors were able to produce bilateral cortical necrosis. The reverse experiment was not performed, but it is of interest to speculate whether, under appropriate conditions, with prolonged medullary ischemia by by-passing of blood into the cortical circuit, it might not be possible to produce the analogue of cortical necrosis, namely necrosis of the renal papillae (figure 5).

It is unlikely, in view of the findings of Trueta's group, that the presence of intracapillary glomerulosclerosis would tend to decrease the blood supply to the renal papilla, as is so commonly supposed, but rather the amount of blood diverted to the medulla may be increased. Further, the degenerative changes in the juxtamedullary glomeruli in elderly persons, culminating in the formation of arteriae rectae verae, all tend to further divert the renal blood flow through the medullary by-pass. Hence, arterial nephrosclerosis may not be considered, theoretically or factually, as a significant factor in compromising the blood supply to the papilla.

*III. Mechanical Factors.* Robbins, S. L., et al.<sup>5</sup> state that papillary ischemia best explains the occurrence of papillary necrosis. They suggest that the marked inflammatory reaction in the diabetics, and the back pressure of urinary tract obstruction, both operate to further mechanically reduce the anatomically inferior blood supply to the papillae by compression of the

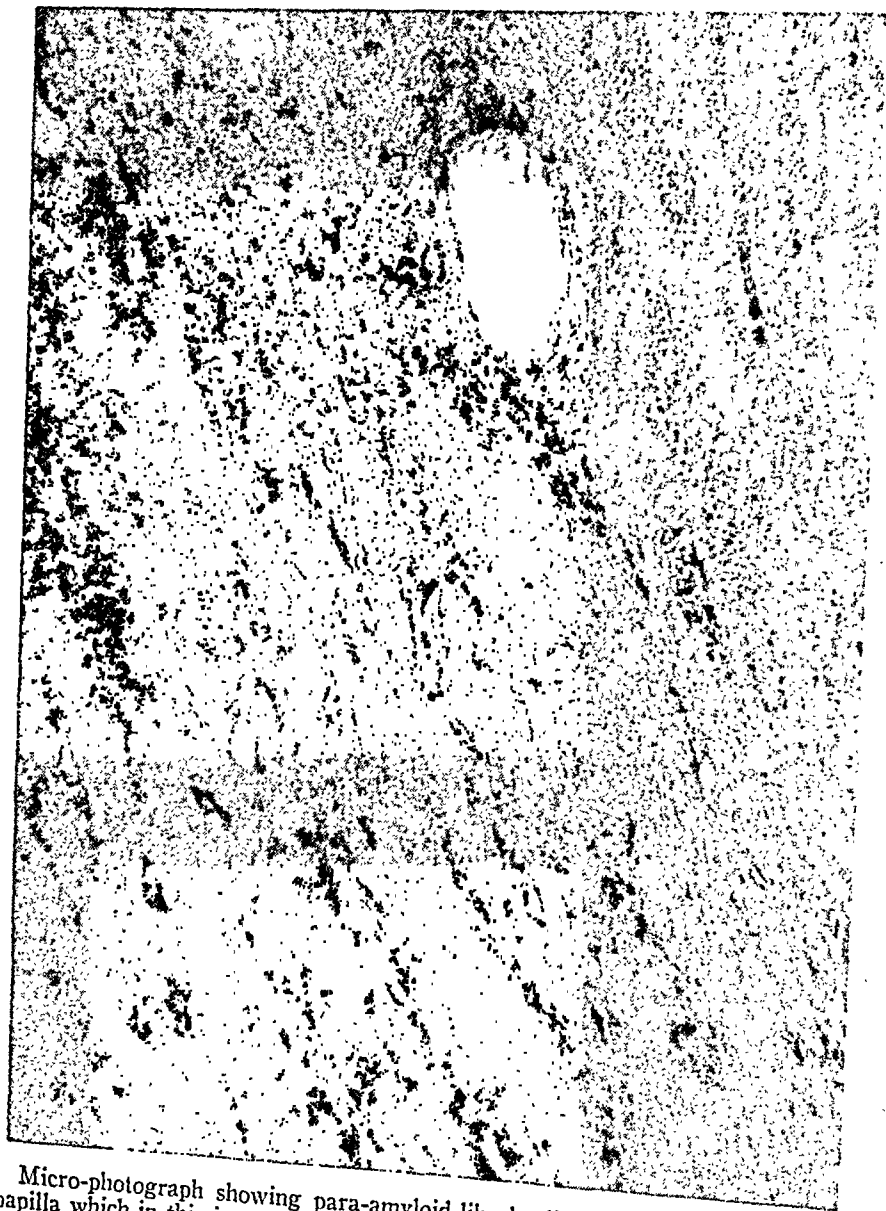


FIG. 7. Micro-photograph showing para-amyloid-like hyalin material in the stroma of the papilla which in this instance bears no direct relationship to necrosis of papillae.

thin wall capillaries. Davson and Langley<sup>18</sup> also discuss the rôle of mechanical pressure, and question why, if pressure on blood vessels were the cause of the necrosis, the lesion is not more often seen in hydronephrosis or nephrolithiasis. Mellgren and Redell<sup>26</sup> consider the deposition of the "para-amyloid" in the interstitial tissue of the renal papillae to play a

mechanical rôle in the production of papillary necrosis, both by pressure and by interference with nutrition of the tubules. We have seen small isolated foci of hyalin material in the papillae of a few of our cases, but have found it more extensively in devitalized papillae of hydronephrotic kidneys, and in sclerotic or senile kidneys than in cases of papillary necrosis (figure 7). The Kimmelstiel-Wilson kidney does not often show papillary necrosis though amyloid-like material is found in increased amounts.

*IV. The Rôle of the Diabetic State.* The diabetic state in some fashion plays an important rôle in the pathogenesis of this lesion. It is generally considered that diabetics have "less resistance" to infection. The presence of acid bodies in the diabetic urine<sup>18</sup> and the extravasation of acid urine through necrotic tubules<sup>1</sup> have been suggested as possible factors. Harrison and Bailey<sup>9</sup> have demonstrated the frequency of asymptomatic urinary tract infections in diabetics. These authors found, in a series of diabetic patients, that over half had bacilluria, and one-fifth had pyuria; and that bacilluria was six to seven times more frequent, and pyuria five times more frequent in diabetics, than in non-diabetics. It would appear then that this factor of latent infection is more commonly present in the production of papillary necrosis in diabetics than in non-diabetics.

The investigations of Menkin<sup>20, 21</sup> have disclosed certain differences in the inflammatory process in diabetics. The local decrease in pH in inflammation is a lactic acid acidosis produced by increased glycolysis. The increase in local proteolysis in inflammation in diabetes implies increased tissue damage. Gangrene is more common and more severe in diabetics, and papillary necrosis can be thought of as but another example of gangrene in this disease.

*V. The Experimental Production of Papillary Necrosis.* Attempts to produce papillary necrosis by producing renal infection with urinary tract obstruction have not been successful. Edmondson et al.<sup>1</sup> tied off the ureter in depancreatized rats. The animals developed a pyonephrosis (whereas only hydronephrosis developed in the non-diabetic rat) but papillary necrosis was not found. In their study on experimental pyelonephritis in rabbits, Mallory, Crane, and Edwards<sup>22</sup> do not describe the lesion of papillary necrosis, although Robbins, S. L., Mallory and Kinney refer to its occurrence in such experimental work.

From a study of our material, we conclude that the sequence of events in the appearance of this lesion is an initial rapid, complete infarct-like necrosis of the entire affected region, followed by an inflammatory reaction. This is first seen in varying intensity from minimal to marked, at the junction between the viable and necrotic tissue. There is usually no inflammatory exudate in the area of necrosis but bacterial colonies are commonly found in the lumina of the dead tubules. With disintegration of the necrotic papilla, a diffuse overgrowth of bacteria occurs. We do not believe that papillary necrosis is produced by the coalescence of small abscesses at the base

of the pyramid with distal ischemic infarction, as described by Robbins, S. L., Mallory and Kinney.

Comparison with necrosis of the papillae produced by chemical poisons<sup>23, 24</sup> confirms the above interpretation, that the lesion is produced by death of tissue en masse, followed by a variable amount of reactive inflammation and bacterial proliferation. Certain specific chemical poisons have successfully produced papillary necrosis in the experimental animal. Levaditi<sup>23</sup> produced the lesion in rabbits, guinea pigs and mice by subacute poisoning with vinylamin. Rehns<sup>24</sup> produced the lesion in rabbits and guinea pigs, but not mice or rats, by administration of tetrahydroquinoline and its methyl esters. The mode of action of these chemicals, and their relation, if any, to fat metabolism, are unknown to us.

The experimental production of papillary necrosis in rats by a fat-free diet has been detailed earlier in this report. It was shown by Burr and co-workers that the deficiency is chiefly one of unsaturated long chain fatty acids; that a very small amount of these may restore normal fat metabolism; and that although the fat-deficient animals synthesize fat, they cannot synthesize the necessary long chain unsaturated fatty acids. It may be very significant that in diabetics there exists a profound disturbance in fat metabolism, with uncontrolled overproduction of fatty acids. The non-diabetics we have studied were all elderly men with chronic urinary tract obstruction and infection, with anemia and azotemia, all of which were additive in producing debility and malnutrition, with its accompanying disturbance of fat metabolism (e.g., "starvation acidosis"). E. M. Boyd<sup>27</sup> found that during fever neutral fat increases 50 per cent, but total and free cholesterol and phospholipids fall, after an initial rise. He noted that the iodine number of plasma fatty acids fell markedly after an initial rise.

It may be said, then, that disturbed fat metabolism is a common factor in diabetes; in non-diabetics with debility, malnutrition, and sepsis; and in the experimental animal on fat-free diet. It is not possible to say at this time whether a deficiency in unsaturated fatty acids plays a direct rôle in the pathogenesis of papillary necrosis, or whether it plays an indirect rôle by inducing alterations in renal hemodynamics, or in the responses to infection.

Although azotemia is commonly found in patients with this lesion, it cannot be the primary mechanism, for papillary necrosis is not commonly found in diseases that produce uremia most commonly, i.e., arteriolar nephrosclerosis, chronic glomerulonephritis, and chronic progressive pyelonephritis. Uremia and azotemia undoubtedly do play a significant part in the debility and malnutrition of these cases. Further, in diabetics, the illness may be fatal within a far shorter time than is found in uremia. It would seem that azotemia and uremia contribute to the lesion but are not its causes, and rather may be caused by it.

Papillary necrosis is not invariably fatal, for healing does occur, as is demonstrated in our case 8; in a case reported by Edmondson et al.<sup>1</sup>; and in

a case described by Günther<sup>2</sup> the course of which was followed by means of retrograde pyelograms over a period of six months.

Nephrectomy has been performed in several instances of this disease. In two operated diabetics reported by Robbins, S. L., et al.,<sup>5</sup> the patients were alive and apparently free of renal disease one year later. In three surgically treated diabetic cases reported by Günther,<sup>2</sup> one died eight weeks later, but the other two survived. Mellgren and Redell<sup>20</sup> describe a case in which the surgically removed kidney showed extensive papillary necrosis. The remaining kidney, at autopsy some time later, revealed much less extensive necrosis of the papillae.

It is unlikely that all of the nephrectomized diabetic patients who survived had only unilateral lesions. It is far more probable that some had bilateral lesions which went on to healing in the remaining kidney. We have seen several cases at autopsy which suggested a preëxisting necrotic papillitis in the form of reticulated or spongy fibrous remnants. The several cases of this group presenting very suggestive transition features are not included in this study of the fully developed acute lesion.

### SUMMARY

1. Necrosis of the renal papillae is a striking pathological lesion which is found in association with acute pyelonephritis in diabetics, and in non-diabetics with urinary tract obstruction.

2. The clinico-pathological findings in 13 acute and one healing case are reviewed.

3. The diabetic patients as a group are younger, have a shorter clinical course, and may present themselves in coma. This may have the appearance of diabetic coma, but acetonuria may be absent. The sex incidence of two females to one male is apparently not explained by higher incidence of diabetes in the female.

4. The non-diabetic patients are older, have a more prolonged clinical course and are usually males with prostatism and urinary tract infection.

5. Experimentally, this lesion has been produced by specific chemical poisons, and by fat-free diets whose essential defect appears to be the absence of certain long chain unsaturated fatty acids.

6. A parallelism is suggested between the disturbed fat metabolism in diabetics, in non-diabetics with urinary tract obstruction and sepsis, and in experimental fatty acid deficiency.

7. It is suggested that papillary necrosis may well be the homologue of cortical necrosis of the kidney on the basis of altered hemodynamics, as indicated by the work of Trueta, with spasm of the medullary vessels rather than the cortical vasculature as the significant factor in the mechanism.

8. Necrosis of the pyramids can go on to complete healing. A single or multiple recurrent attacks of such papillary necrosis, with subsequent healing and epithelization, may represent one mechanism of hydronephrosis.

BIBLIOGRAPHY

1. EDMONDSON, H. A., MARTIN, H. E., and EVANS, N.: Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus, *Arch. Int. Med.*, 1947 lxxix, 148-175.
2. GÜNTHER, G. W.: Die Papillennekrosen der Niere bei Diabetes, München. med. Wchnschr., 1937, lxxxiv, 1695-1699.
3. ALKEN, C. E.: Die Papillennekrose, *Ztschr. f. Urol.*, 1938, xxxii, 433-438.
4. PELLEGRIN, F. A.: Necrotizing renal papillitis, *Permanente Foundation Med. Bull.*, 1947, v, 66-74.
5. ROBBINS, S. L., MALLORY, G. K., and KINNEY, T. D.: Necrotizing renal papillitis: a form of acute pyelonephritis, *New England Jr. Med.*, 1946, ccxxxv, 885-893.
6. HARRISON, J. H., and BAILEY, O. T.: Significance of necrotizing pyelonephritis in diabetes mellitus, *Jr. Am. Med. Assoc.*, 1942, cxviii, 15-20.
7. BURR, G. O., and BURR, M. M.: New deficiency disease produced by rigid exclusion of fat from diet, *Jr. Biol. Chem.*, 1929, lxxxii, 345-367.
8. BURR, G. O., and BURR, M. M.: On the nature and rôle of fatty acids essential in nutrition, *Jr. Biol. Chem.*, 1930, lxxxvi, 587-621.
9. WESSON, L. G., and BURR, G. O.: Metabolic rate and respiratory quotients of rats on fat-deficient diet, *Jr. Biol. Chem.*, 1931, xci, 525-539.
10. BURR, G. O., BURR, M. M., and BROWN, W. R.: On nutritive value of certain oils, *Proc. Soc. Exper. Biol. and Med.*, 1931, xxviii, 905-907.
11. BURR, G. O., BURR, M. M., and MILLER, E. S.: On fatty acids essential in nutrition, *Jr. Biol. Chem.*, 1932, xcvi, 1-9.
12. BURR, G. O., and BROWN, W. R.: On fatty acids essential in nutrition, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1349-1352.
13. HANSEN, A. E., and BURR, G. O.: Studies on iodine absorption of serum in rats fed on fat-free diets, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1200-1201.
14. HANSEN, A. E., and BURR, G. O.: Iodine numbers of serum lipids in rats fed on fat-free diets, *Proc. Soc. Exper. Biol. and Med.*, 1933, xxx, 1201-1203.
15. BURR, G. O., and BEBER, A. J.: Metabolism studies with rats suffering from fat deficiency, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxi, 911-912.
16. BURR, G. O., BROWN, J. B., KASS, J. P., and LUNDBERG, W. O.: Comparative curative values of unsaturated fatty acids in fat deficiency, *Proc. Soc. Exper. Biol. and Med.*, 1940, xlii, 242-244.
17. BORLAND, V. G., and JACKSON, C. M.: Effects of fat-free diet on structure of kidney of rats, *Arch. Path.*, 1931, xi, 687-708.
18. DAVSON, J., and LANGLEY, F. A.: Papillitis renis necroticans, *Jr. Path. and Bact.*, 1944, lvi, 327-333.
19. SHEEHAN, H. L.: Medullary necrosis of kidneys, *Lancet*, 1937, ii, 187-189.
20. MENKIN, V.: Biochemical factors in inflammation and diabetes mellitus, *Arch. Path.*, 1942, xxxiv, 182-195.
21. MENKIN, V.: On mechanism of enhanced diabetes with inflammation, *Am. Jr. Physiol.*, 1941, cxxxiv, 517-541.
22. MALLORY, G. K., CRANE, A. R., and EDWARDS, J. E.: Pathology of acute and healed experimental pyelonephritis, *Arch. Path.*, 1940, xxx, 330-347.
23. LEVADITI, C.: Recherches expérimentales sur la nécrose de la papille rénale, *Arch. internat. de pharmacodyn. et de therap.*, 1901, viii, 45-63.
24. REHNS, J.: D'une nécrose typique de la papille rénale déterminée par la tétrahydroquinoléine et certains de ses dérivés, *Arch. internat. de pharmacodyn. et de therap.*, 1901, viii, 199-202.
25. TRUETA, J., et al.: Studies of the renal circulation, 1947, Blackwell, Oxford, Pp. 187.
26. MELLGREN, J., and REDELL, G.: Zur Pathologie und Klinik der Papillitis necroticans renalis, *Acta chir. Scandinav.*, 1941, lxxxiv, 439-457.
27. BOYD, E. M.: Lipopenia of fever, *Canad. Med. Assoc. Jr.*, 1935, xxxii, 500-506.



# THE SURGICAL TREATMENT OF BLEEDING ESOPHAGEAL VARICES BY PORTAL SYSTEMIC VENOUS SHUNTS WITH A REPORT OF 34 CASES \*

By ROBERT R. LINTON, M.D., F.A.C.S., *Brookline, Massachusetts*

ESOPHAGEAL varices develop spontaneously because of obstruction to the return of the portal blood to the systemic venous system. The site of the portal bed block may be either in the liver, the intrahepatic type secondary to portal cirrhosis, or in the portal vein itself, the extrahepatic type, as seen in the so-called Banti's syndrome (table 1). The block in the former develops as a result of scarring in the liver parenchyma. It occurs most frequently in cases of alcoholic and other forms of toxic cirrhosis and is the more common type. Thrombosis of the hepatic vein is another cause of the intrahepatic type of block. It is relatively rare, however. The portal bed block in the extrahepatic type may result from a congenital obliteration of the portal vein

TABLE I  
Types and Etiology of Portal Bed Block  
(Massachusetts General Hospital)

- I. Intrahepatic
  - A. Portal cirrhosis (Laennec type)
    - 1. With cavernomatous transformation of portal vein
    - 2. Without cavernomatous transformation of portal vein
  - B. Thrombosis of hepatic veins
- II. Extrahepatic (Banti's syndrome)
  - A. Congenital—oblit. of portal v. with cavernomatous transformation
  - B. Acquired—thrombosis of the portal vein or its tributaries
    - 1. Infectious      2. Traumatic      3. Spontaneous
- III. Combined type
  - Portal cirrhosis with portal vein thrombosis

or arise secondary to thrombophlebitis of the portal venous system, the etiology of which may be traumatic, infectious or idiopathic. A combined form of the intrahepatic and extrahepatic types has been found in a certain number of cases. In this group of patients a thrombophlebitis of the portal venous system has apparently developed secondary to the intrahepatic block due to cirrhosis of the liver. Whipple<sup>1</sup> describes another form of extrahepatic block, the so-called cavernomatous transformation of the portal vein, which is thought by some authorities to represent a vascular neoplastic lesion, an angioma in the hepatoduodenal ligament. It seems more likely, however, that the innumerable small blood vessels encountered in this region probably represent collateral channels that have developed as a result of the block in

\* Presented at the Thirtieth Annual Session of the American College of Physicians, New York, N. Y., March 31, 1949.

From the Departments of Surgery of the Harvard Medical School and the Massachusetts General Hospital, Boston, Massachusetts.

the portal venous system, since this type of vascular pathology has been found both in the intra- and extrahepatic groups.

The normal venous pressure in the portal system is higher than in the systemic veins because the portal blood after passing through the capillaries of the gastrointestinal tract, spleen and pancreas must traverse another capillary bed, the liver sinusoids, before it enters the inferior vena cava. The normal portal venous pressure has been found to be 10 to 15 cm. of saline. In the presence of portal bed block, either intra- or extrahepatic, the state of so-called portal hypertension develops with pressures varying from 25 to 50 cm. of saline. One of the collateral channels whereby the portal blood returns to the systemic venous system in these conditions is the esophageal veins. These vessels do not anastomose freely with the systemic system so that they frequently become greatly enlarged and varicosed. Hemorrhage from them is a common complication of portal hypertension and carries with it a very high mortality rate. The cause of rupture of these blood vessels has not been satisfactorily explained, but in part it is believed due to the relatively high venous pressure within them. Wangensteen<sup>2</sup> has suggested that it may be due to peptic ulceration of the esophageal mucosa over them, because of the reflux of acid gastric contents into the esophagus.

#### DIAGNOSIS

The diagnosis of bleeding esophageal varices should be considered along with the other causes of esophageal-gastrointestinal bleeding in any patient who gives a history of hematemesis or melena. A sudden massive hematemesis is frequently the first sign that a patient has a portal bed block, especially of the extrahepatic type, since there are few premonitory symptoms of the disease. The diagnosis of a portal bed block with esophageal varices is suggested by such a history, especially if an enlarged spleen is found on physical examination. The blood, as a rule, shows a secondary anemia, a leukopenia and a thrombocytopenia. If the block is intrahepatic the liver may be shrunken, normal or enlarged and in the extrahepatic it is usually normal in size. The two types may be further differentiated by liver function tests. When the block is intrahepatic, there is usually a high retention of bromsulfalein, a reversal of the albumin-globulin ratio with a low level of serum albumin, a positive cephalin flocculation test and an elevated prothrombin time. If the block is extrahepatic all these liver function tests are usually normal. The most important diagnostic procedure, however, in patients suspected of having bleeding esophageal varices is a roentgenologic examination of the esophagus with a thick suspension of barium, as first described by Wolf<sup>3</sup> and later Schatzki<sup>4</sup> (figure 1). The visualization of the blood vessels by this technic depends to a great extent on the skill of the roentgenologist. Direct visualization of the lower end of the esophagus by esophagoscopy is another aid in diagnosis. The demonstration of esophageal

varices by either of these methods indicates the presence of portal hypertension secondary to either an intra- or an extrahepatic portal bed block.

The frequency with which bleeding occurs from esophageal varices has been variously reported. Preble<sup>5</sup> in 1900 in reviewing 60 cases of fatal gastrointestinal bleeding found that 80 per cent had esophageal varices. Macroscopic evidence of rupture of these vessels was demonstrated in 50 per cent. Rivers and Wilbur<sup>6</sup> in 1932 reported that in a group of 668 patients with a history of hematemesis the bleeding was secondary to cirrhosis of the

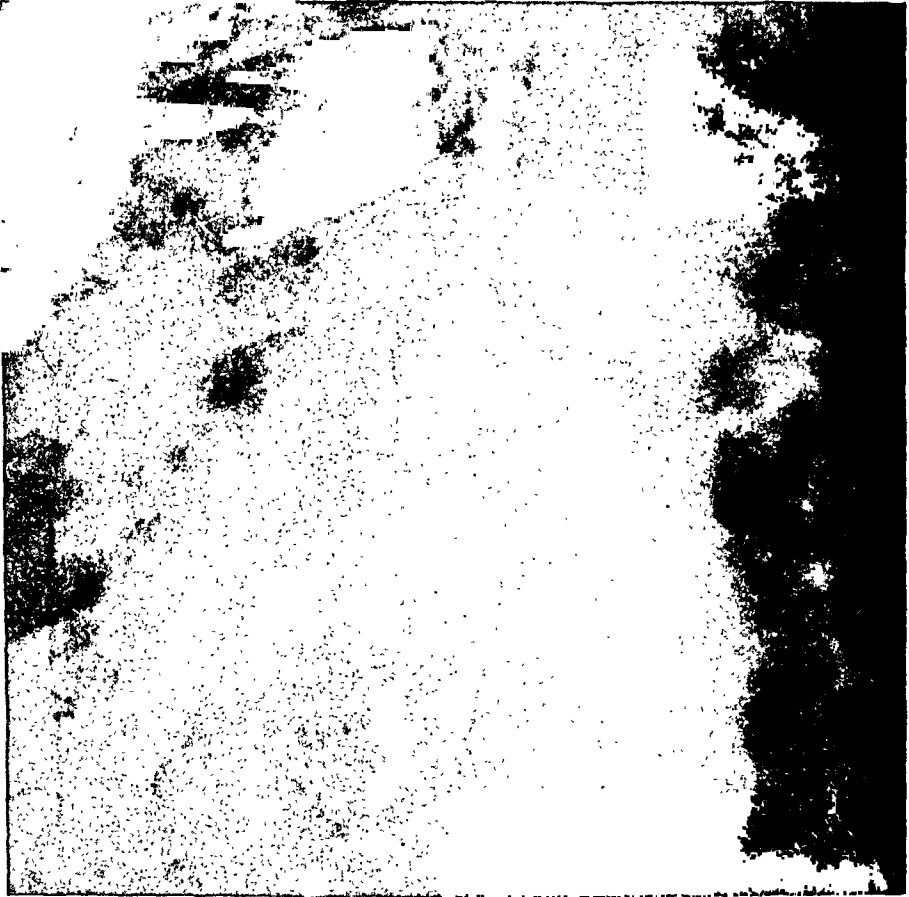


FIG. 1. A reproduction of a roentgenogram of the esophagus demonstrating the esophageal varices in a patient with portal hypertension due to so-called Banti's syndrome. This diagnostic procedure affords the most positive diagnosis of portal hypertension.

liver, or splenic anemia (Banti's syndrome), in 33, or 5 per cent. A recent analysis by Costello<sup>7</sup> in 1949 of 300 consecutive cases of massive hematemesis reveals that 24, or 8 per cent of the series, had ruptured esophageal varices as the cause. It is extremely significant and pertinent to this discussion that 19 died from hemorrhage, a mortality rate of 71 per cent, in this group.

Shull<sup>8</sup> in 1947 studied 108 patients with cirrhosis of the liver and 20 patients with Banti's syndrome that were admitted to the Massachusetts

General Hospital over a 12 year period from 1934 to 1945. He found that in the cirrhotic group only 40, or 37 per cent, were alive one year after the diagnosis of esophageal varices was made. In the Banti's syndrome group 18, or 90 per cent, were alive. This higher mortality rate in the patients with cirrhosis is due undoubtedly to the fact that the patients are in an older age group. In addition and of extreme importance is the fact that they for the most part have severely damaged livers, whereas the Banti's group are relatively young and have essentially normal livers. Shull<sup>8</sup> in these same patients found that in the cirrhotic group 90, or 83 per cent, died from all causes. Of extreme significance, however, he found that 41, or 45 per cent, of those that died succumbed to massive esophago-gastrointestinal hemorrhage. In the Banti's group, seven, or 35 per cent, died from all causes and of these five, or 71 per cent of the deaths were due to hemorrhage. The mortality rates from hemorrhage alone in all the patients of the two groups were 38 per cent for the cirrhotics and 25 per cent for the Banti's syndrome group. In addition it is believed that hemorrhage was an important contributing factor in the death of many of the other patients who died from liver failure and other causes. This is especially apt to be true in a group with intrahepatic block, because in many of these patients the serum albumin level is already low due to the liver disease, and as a result of the severe hemorrhage a further rapid reduction takes place. Moreover in the presence of a diseased liver restoration of the serum albumin to a normal level seldom occurs.

The analysis of these cases is of great significance, since it demonstrates the grave prognosis once esophageal varices are diagnosed and the high mortality rate due to hemorrhage from them. At best bleeding esophageal varices cause prolonged disability, since patients after severe hemorrhage frequently require many weeks to months of hospitalization with expensive therapeutic measures. Numerous blood transfusions are essential in many cases to prevent death from shock, and in some cases the blood escapes almost as fast or faster than it can be administered. Under such conditions the bleeding may only be stopped by the placing of a balloon in the stomach which, after inflation, is drawn up against the cardia by means of traction on the rubber tube to which the balloon is attached, as reported by Rowntree et al.<sup>9</sup>

✓ The realization of this high morbidity and mortality due to the bleeding from esophageal varices has spurred us on in an attempt to lower the portal hypertension and reduce the amount of blood in the esophageal varices by formation of various types of portal systemic venous shunts. The treatment of bleeding esophageal varices by various surgical procedures has been attempted for many years. The demonstration by Eck<sup>10</sup> in 1877 that the portal venous blood could be shunted directly into the systemic venous system by anastomosing the portal vein directly to the inferior vena cava in experimental animals, thereby by-passing the liver, stimulated surgeons in the latter part of the 19th century and the early part of the 20th century to perform

a similar type of shunt in human patients. Few were successful, presumably because of the high mortality rate from the operative procedure, so that this method of treatment was abandoned for several decades. It was not until the recent work of Whipple<sup>1</sup> and Blakemore and Lord<sup>11</sup> in 1945, who reported the successful construction of portacaval shunts, that surgeons became interested again in this relatively unexplored field in vascular surgery. These authors first described an end-to-end splenorenal type of shunt, utilizing the nonsuture type of blood vessel anastomosis with the vitallium tube method of Blakemore and Lord.<sup>11</sup> In addition to performing a splenectomy at the same time, it was also necessary to sacrifice the left kidney in order to perform this type of a shunt.



FIG. 2. An artist's drawing showing the completed end-to-side suture type of splenorenal anastomosis with preservation of the left kidney. 1. splenic vein; 2. renal artery; 3. suprarenal vein; 4. spermatic vein; 5. renal vein; 6. left kidney. (Courtesy Surg. Clin. N. Am., W. B. Saunders Co., 1947, xxvii, 1162.)

The above procedure has been modified by the construction of an end-to-side splenorenal anastomosis with preservation of the kidney, as previously reported<sup>12, 13</sup> (figure 2). This operation is preferred, first because it produces a partial shunt of the portal blood flow, so that the liver is not completely by-passed. Second, because our observations indicate that this type of shunt appears to lower satisfactorily the portal hypertension. Third, the splenectomy reduces the arterial inflow to the portal area by approximately 20 to 40 per cent and thereby aids in the reduction of the portal hypertension. Fourth, the end-to-side type of anastomosis in addition to preserving the kidney has the advantage that it is less apt to become thrombosed. Fifth, it can be constructed by the suture technic instead of the nonsuture vitallium

tube method, thereby reducing the incidence of thrombosis at the site of the anastomosis. Sixth, there are no vital structures in the left upper quadrant of the abdomen, the region through which the surgical approach is made for this type of shunt, similar to the common bile duct or the hepatic artery which lie in such close proximity to the region where it is necessary to dissect out the portal vein and the inferior vena cava to perform a direct portacaval anastomosis. This last is a point of great practical importance since in either type of shunt operation structures are obscured frequently by bleeding from innumerable small collateral venous channels. An error of a few millimeters in the region of the gastrohepatic ligament in searching for the portal vein may irreparably damage the common bile duct or the hepatic artery with serious consequences, whereas in the splenic area such catastrophes are not as likely to occur since the margin of safety in this region can be measured in centimeters rather than millimeters.

During the past four years at the Massachusetts General Hospital from 1945 to 1948 inclusive, 34 patients with portal hypertension have had various types of portal systemic venous shunts constructed by the suture technic for bleeding esophageal varices. These operative procedures have not been performed on patients unless there was a history of esophago-gastrointestinal bleeding, nor have they been done for the relief of ascites alone. It has been considered advisable in developing this new type of surgery to subject only those patients in whom severe or repeated hemorrhages have taken place in an attempt to see whether future bleedings could be prevented. In this group of patients there were 20 with the intrahepatic type of portal bed block due to cirrhosis of the liver and 14 patients with Banti's syndrome, or congestive splenomegaly, the extrahepatic type of portal bed block. The youngest patient in the group was six years of age and the oldest 65 years. Both had the extrahepatic type of portal bed block, the former presumably of congenital origin due to obliteration of the portal vein and the latter due to thrombosis of the portal venous system of idiopathic origin. The mean age in this group was 36 years. The ages of the intrahepatic group due to cirrhosis of the liver ranged from 27 years to 60 years with a mean age of 44 years. Seven patients in the latter group died as a result of the operative procedure, a mortality rate of 35 per cent. There were no deaths in the Banti's syndrome group, making an operative mortality rate of 21 per cent for the entire group. It is of interest that the operative mortality rate has dropped with the increased experience gained in this type of surgery and the better selection of patients for the procedure, since 20 patients were operated upon in the year 1948 with two deaths, an operative mortality rate of only 10 per cent. Both of them occurred in the cirrhotic group. These statistics indicate, as might be expected, that the risk of this type of surgery which frequently requires four to six hours of anesthesia is greater in those patients with cirrhosis because of the underlying liver disease.

An analysis of the causes of death in these seven patients reveals that four of them died within a few hours of uncontrollable hemorrhage from the

site of operation due to a state of incoagulability of the blood. The preoperative prothrombin times were normal in all these patients and for the first two hours of the operation in each case there was no evidence of the failure of the patient's blood to clot. However, after varying periods from two to three hours after the operation was commenced it was noted that blood began to ooze from all the cut surfaces of the operative site. Samples of blood collected in test tubes failed to clot for many hours and when these were recalcified there was still no evidence of clotting, indicating that it was not caused by the sodium citrate in the blood transfusions. Further studies are in progress at the present time in an effort to determine the cause of this phenomenon which ended so disastrously in these four patients. All of them had severely damaged livers from cirrhosis. Because of this a more careful selection of patients is now made, especially in reference to the condition of the liver, in an effort to prevent similar tragedies, as Blakemore<sup>14</sup> has also stressed. The other three patients died from various causes: one from massive esophageal bleeding five days following an anastomosis of the superior mesenteric vein to the inferior vena cava. (At operation in this case the superior mesenteric vein was obviously not of sufficient caliber to lower satisfactorily the portal hypertension.) Another case died 48 hours postoperatively from liver failure; the third one in 48 hours, secondary to thrombosis of the hepatic artery. This group of seven deaths is extremely regrettable but when it is realized that most of these patients were extremely ill and were operated on as a last resort in an attempt to save their lives, it is not too surprising that some of them did not survive a surgical operation of the magnitude of these shunt procedures.

A splenectomy with an end-to-side suture type of splenorenal anastomosis has been the most common type of shunt performed in our clinic. It was performed in 26, or 74 per cent, of the patients. There were four postoperative deaths, an operative mortality of 15 per cent. Twenty-two patients, or 85 per cent, survived the operation. One patient, a man aged 60, with cirrhosis of the liver, succumbed to liver failure secondary to alcoholism eight months following the formation of the splenorenal shunt. He had not bled since it was performed and postmortem examination revealed a satisfactory patent venous anastomosis without evidence of old or recent thrombosis. Esophago-gastrointestinal bleeding has occurred in one of the 21 surviving patients, an incidence of postshunt bleeding of approximately 5 per cent. This patient is one of the Banti's syndrome group and was the first one on whom the splenorenal type of shunt was performed. The bleeding followed an overindulgence in food and alcoholic beverages. Another factor in this patient which might explain the postoperative bleeding was that the end-to-side splenorenal anastomosis was of inferior construction as it was the first one performed. Moreover great technical difficulties were encountered at the operation, due to the fact that there had been three previous operative procedures, including first: a ligation of the splenic artery and an omento-

pexy; second, ligation of the coronary vein of the stomach and a second omentopexy; and third, a transthoracic ligation of the peri-esophageal veins.

A direct portacaval shunt, the Eck type of fistula, anastomosing the portal vein to the inferior vena cava was attempted in eight patients. It was possible to perform it in only three of them because in the other five the extreme vascularity in the region of the gastrohepatic ligament prevented exposure of the portal vein. In one patient the common bile duct and gall bladder were injured, necessitating a choledochojejunostomy to reestablish the flow of bile into the intestinal tract and also a cholecystectomy. This patient at a later operation had a splenectomy and a satisfactory end-to-side splenorenal shunt performed. The direct portacaval type of anastomosis was chosen in these eight patients for various reasons. Splenectomy had been previously performed in five of them, which has been found to preclude the construction of a splenorenal shunt at a later date because of thrombosis and secondary fibrosis of the splenic vein. For this reason it was necessary to attempt some other form of shunt in these patients and the direct portal vein to inferior vena cava type of anastomosis was chosen. In two other patients this procedure was selected because the spleen in both was only slightly enlarged, indicating that the splenic vein would not be large enough with which to create a shunt of sufficient size to reduce the portal hypertension. In the remaining patient it was chosen because three other surgeons who had operated upon him had considered a splenectomy to be too formidable a procedure to perform, so that a direct portacaval shunt was attempted almost of necessity. It is of interest that the portal bed block was intrahepatic in three of the patients and extrahepatic in the other five. Two of the patients died; one in whom the shunt was constructed succumbed because of thrombosis of the hepatic artery, the result of operative trauma. In the other one the operation had to be discontinued even before the portal vein was exposed because of uncontrollable bleeding in the operative field and despite numerous transfusions the patient died from postoperative hemorrhage. Both of these patients had the intrahepatic type of portal bed block with severe impairment of liver function from portal cirrhosis, which undoubtedly played some rôle in their deaths.

A successful portacaval anastomosis with survival was performed in only two of the patients, one with intrahepatic block and the other of the extrahepatic type. Both of these patients had had previous splenectomies without relief from massive bleeding. It is at least encouraging that they are alive and have had no further esophago-gastrointestinal hemorrhages for periods of six months in one case and 12 months in the other. The difficulty encountered in attempting to perform a portal vein to inferior vena cava shunt in patients with the so-called Banti's syndrome, the extrahepatic type of portal bed block, who have had previous splenectomies cannot be over-emphasized, as has already been reported,<sup>15</sup> since in four of these previously splenectomized patients it was possible only in one to create a satisfactory shunt.



In view of these facts and also the good results obtained to date with spleno-renal shunts, it should be stressed that a surgeon, who does a splenectomy for portal hypertension, especially for patients with Banti's syndrome, should perform a spleno-renal anastomosis at the same operation, since this may be the only opportunity for the construction of a satisfactory shunt.

It is of interest also that in three patients, previously splenectomized, in whom a direct portacaval anastomosis was impossible, other types of shunts have been performed (figure 3). An anastomosis between the proximal end

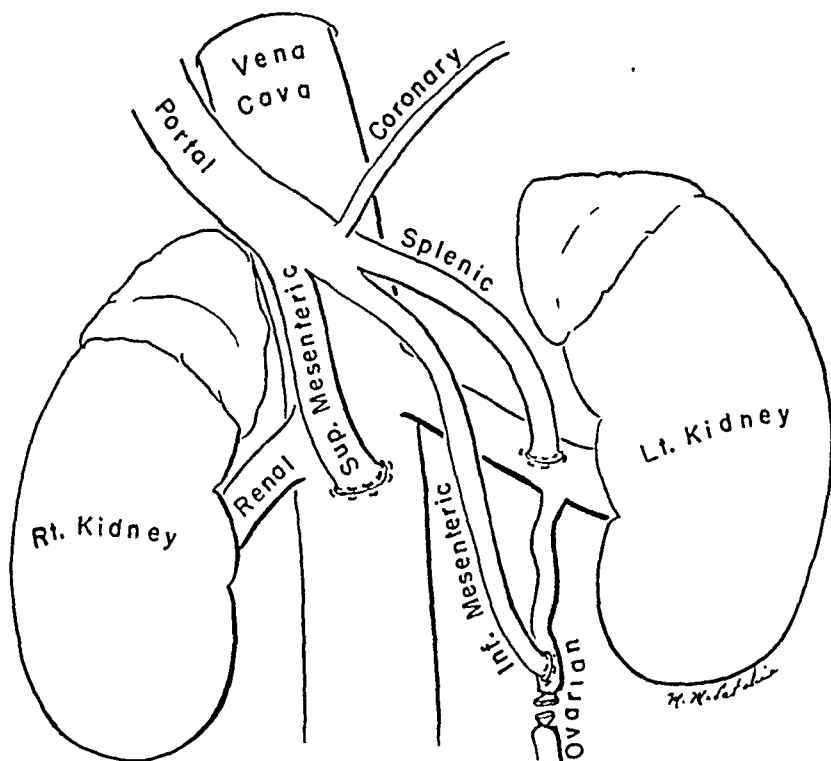


FIG. 3. An artist's schematic drawing showing various types of portal systemic venous shunts. The end-to-side spleno-renal anastomosis is preferred, but in two patients who had had previous splenectomies a superior mesenteric to inferior vena cava anastomosis was performed in one and in the other an inferior mesenteric to left ovarian vein anastomosis was used because it was not possible to isolate the portal vein in either due to the extreme degree of vascularity in the gastrohepatic ligament. (Courtesy Surg., Gynec. and Obst., 1948, lxxxvii, 129.)

of the superior mesenteric vein at the base of the mesentery and the inferior vena cava was performed in one of these patients. In another the inferior mesenteric vein was anastomosed to the left adrenal vein and in a third this vessel was anastomosed to the left ovarian vein. These types of shunts are considered to be makeshift ones at best, since these tributaries of the portal vein are too small to produce an anastomosis of sufficient size to reduce the portal hypertension satisfactorily. Nevertheless, although all three patients have had further esophago-gastrointestinal bleeding episodes, they have been

improved since the postshunt episodes of hemorrhage have not been as severe as the prior ones.

In summary, it can be stated that the construction of various types of portal systemic venous shunts represents a new chapter in the treatment of bleeding esophageal varices, a condition which heretofore has failed to respond to other forms of treatment. In the four year period from 1945 to 1948 inclusive, 34 patients at the Massachusetts General Hospital have been subjected to this type of surgery because of the chief complaint of massive esophago-gastrointestinal hemorrhages. The chief benefit from this type of procedure, that has been observed to date, has been the cessation of bleeding in a majority of patients that have had a satisfactory shunt performed, either a direct portacaval or a splenorenal type. There are 24 patients in this group that can be classified in this category and only one of them has bled since the operation was performed, an incidence of only 4 per cent of bleeding.

The postoperative follow-up studies in reference to liver function at present are incomplete. The bromsulfalein retention test and the serum albumin level in the cirrhotic group of patients reveals little if any improvement in these functions of the liver. In the Banti's syndrome group, they reveal little if any impairment following the construction of the shunt. The cephalin flocculation test in the majority of the cirrhotic patients shows slight improvement from  $4 + - 3 +$  to  $3 + - 2 +$ . The most striking improvement has been in the level of the hemoglobin, as would be expected, since esophago-gastrointestinal bleeding has ceased in the majority of patients. The pre-operative levels varied from 7.4 to 12.4 grams of hemoglobin per 100 cubic centimeters of blood and the postoperative levels have been maintained at from 11 to 17.5 grams of hemoglobin. The period of postoperative follow-up is of necessity short, but it ranges from four to 34 months. A true evaluation of the procedure necessarily must await a greater lapse of time, but at the present writing the results are definitely encouraging.

### CONCLUSIONS

1. The establishment of portal systemic venous shunts represents a new and encouraging chapter in the treatment of bleeding esophageal varices secondary to portal hypertension.

2. Splenectomy and the suture type of end-to-side splenorenal anastomosis with preservation of the kidney is recommended as the most satisfactory operative procedure.

3. It is believed that a surgeon should not do a splenectomy in a case of portal hypertension unless he is prepared to do a splenorenal anastomosis at the same operation, since this may be the only opportunity to construct a satisfactory portal systemic venous shunt.

4. The postoperative studies over periods of 4 to 34 months in patients in whom satisfactory portal systemic venous shunts have been performed

reveal an encouraging cessation in bleeding from the esophago-gastrointestinal tract and the maintenance of normal hemoglobin levels in the blood.

5. A true evaluation of this method of treatment for bleeding esophageal varices, secondary to portal hypertension, must await a longer period of observation of the patients that have been treated by this method.

#### BIBLIOGRAPHY

1. WHIPPLE, A. O.: Problem of portal hypertension in relation to hepatosplenopathies, *Ann. Surg.*, 1945, cxxii, 449.
2. WANGENSTEEN, O. H.: The ulcer problem (Listerian oration), *Canad. Med. Assoc. Jr.*, 1945, liii, 309.
3. WOLF, G.: Die Erkennung von Ösophagus-Varizen im Röntgenbilde, *Fortschr. a.d. Geb. d. Röntgenstr.*, 1928, xxxvii, 890.
4. SCHATZKI, R.: Roentgen demonstration of esophageal varices—its clinical importance, *Arch. Surg.*, 1940, xli, 1084.
5. PREBLE, R. B.: Conclusions based on sixty cases of fatal gastro-intestinal hemorrhage due to cirrhosis of the liver, *Am. Jr. Med. Sci.*, 1900, cxix, 263.
6. RIVERS, A. B., and WILBUR, D. L.: The diagnostic significance of hematemesis, *Jr. Am. Med. Assoc.*, 1932, cxxxv, 1629.
7. COSTELLO, C.: Massive hematemesis—analysis of 300 consecutive cases, *Ann. Surg.*, 1949, cxxix, 289.
8. SHULL, H. J.: Personal communication of unpublished data.
9. ROWNTREE, L. G., ZIMMERMAN, E. F., TODD, M. H., and AJAC, J.: Intra-esophageal venous tamponade. Its use in a case of varical hemorrhage from the esophagus, *Jr. Am. Med. Assoc.*, 1947, cxxxv, 630.
10. ECK, N. V.: The ligature of the portal vein, *Voyenno Med. Jr. St. Petarb.*, 1877, i, 130.
11. BLAKEMORE, A. H., and LORD, J. W., JR.: The technic of using vitallium tubes in establishing portacaval shunts for portal hypertension, *Ann. Surg.*, 1945, cxxii, 476.
12. LINTON, R. R., JONES, C. M., and VOLWILER, W.: Portal hypertension—the treatment by splenectomy and splenorenal anastomosis with preservation of the kidney, *Surg. Clin. N. Am.*, 1947, xxvii, 1162.
13. LINTON, R. R., HARDY, I. B., JR., and VOLWILER, W.: Portacaval shunts in the treatment of portal hypertension—an analysis of 15 cases with special reference to the suture type of end-to-side splenorenal anastomosis with splenectomy and preservation of the kidney, *Surg., Gynec. and Obst.*, 1948, lxxxvii, 129.
14. BLAKEMORE, A. H.: Indications for portacaval anastomosis—analysis of cases, *Surg., Gynec. and Obst.*, 1947, lxxxiv, 645.
15. LINTON, R. R.: Portacaval shunts in the treatment of portal hypertension, *New Eng. Jr. Med.*, 1948, ccxxxviii, 723.

# PHARMACODYNAMICS OF PULMONARY ABSORPTION IN MAN. II. THE INFLUENCE OF VARIOUS DILUENTS ON AEROSOL AND INTRATRACHEAL PENICILLIN \*

By JOHN F. BEAKEY, EDWARD A. GAENSLER and MAURICE S. SEGAL, F.A.C.P., *Boston, Massachusetts*

THE pharmacodynamics of pulmonary absorption has not been generally considered in the clinical reports on the success of aerosol and intratracheal therapy. There is equally meager information regarding the action of various pharmacologically active diluents in promoting or retarding absorption of penicillin from the pulmonary epithelium.

In a recent study<sup>1</sup> we described various factors influencing absorption from the normal human lung. Crystalline penicillin G potassium (100,000 units) in physiologic saline was administered intramuscularly, intratracheally and by oxygen-aerosolization. The blood levels and urinary excretion, following intratracheal injection, were lower but more sustained than those following intramuscular administration. Rapid absorption would normally be expected from such a large and vascular area as the alveolar bed. The lung was thus demonstrated as a reservoir capable of considerably retarding the expected rate of absorption. By comparing the total urinary excretion of the intratracheal with aerosol method of administration, the amount of penicillin actually reaching the lung by the latter route was calculated to be about 35 per cent. Easily determinable wastage, occurring during aerosolization, accounted for some of the loss.

Although physiologic saline has been most generally used as the diluent or vehicle for penicillin aerosolization, other diluents, which are active substances themselves, have been suggested. Inhalation of 0.5 to 1 per cent adrenalin has been notably effective in relieving bronchospasm in the asthmatic;<sup>2,3</sup> neosynephrin is a potent bronchovasoconstrictor which shrinks mucous membranes rapidly. Combination of either or both of these two solutions with penicillin was a natural development when the need arose for such medication in addition to penicillin itself. While such vehicles have been used with penicillin, others suggest themselves as effective diluents because of their inherent pharmacological activity. The search for diluents which might either enhance or supplement the action of penicillin or act independently to advantage has attracted relatively few investigators.

\* Received for publication September 11, 1948.

From the Department of Inhalational Therapy, Boston City Hospital and the Department of Medicine, Tufts College Medical School.

This study was aided by a grant from the Commercial Solvents Corporation.

## METHODS

The study was done with the help of normal male volunteers. A standard dose of 100,000 units of crystalline penicillin G potassium was used. Two routes of administration were investigated: intratracheal and inhalational. The technic of administration by each of these routes was the same as previously described.<sup>1</sup> For aerosol administration penicillin was dissolved in 1 c.c. of the diluent. After complete aerosolization, another 0.5 c.c. of the diluent or saline was added to salvage any penicillin clinging to the wall of the nebulizer. We chose this technic, rather than multiple rinsings, to more closely simulate clinical conditions. The Vaponefrin nebulizer was used throughout with an oxygen flow of 5 liters per minute. For intratracheal injection, the penicillin was dissolved in 10 c.c. of the diluent. Diluents with sympathomimetic action were given in lower concentrations by this route than by the aerosol one. Following inhalation, serum was assayed for penicillin activity at the end of one-half, one and two hours; urine specimens, at one, two and 24 hours. Following intratracheal administration, bloods were taken at one-half, one and every hour thereafter for six hours and urine specimens were collected at one, two, four, six and 24 hours.

Using the hemolytic streptococcus No. 98, the serial dilution method of Rammelkamp<sup>4</sup> was employed. The smallest amount of penicillin detectable by this method is 0.02 unit per c.c. of serum. The limits of its accuracy are similar to other methods of biological assay involving serial dilution; each level indicates about one-half as much activity as a positive reaction occurring in the next higher tube. The values are obtained by serial half dilution dividing the number of units per c.c. of standard (20 by 2), i.e. 10, 5, 2.5, 1.25, 0.625, 0.312, 0.156, 0.078, 0.039, 0.019. For purposes of simplicity, we employ values numerically expressed as 0.63, 0.32, 0.16, 0.08, 0.04, etc. A level of 0.04 (0.039) unit of penicillin per c.c. of serum, by this method, inhibits most gram-positive pathogenic organisms.<sup>5</sup>

A total of 837 specimens were assayed—468 sera and 369 urines. The following diluents were studied: saline, neosynephrin, epinephrine, tri-ethylene glycol, chlorophyll, Pantopaque and human serum. These are divided into two main groups: (1) those whose predominant action is on the musculature and vascular bed of the lung, thereby secondarily affecting penicillin absorption, and (2) those which influence absorption by direct chemical or mechanical action. Any one substance may easily influence absorption by a combination of these mechanisms. Each solution is classified, however, according to its presumed predominant effect. Even though the pulmonary vessels are considered to be less responsive to vascular agents than other vessels,<sup>6</sup> substances such as neosynephrin and epinephrine may still be expected to exert some influence on the absorptive mechanism. The other substances studied, as far as is known, do not exert any marked effect on the mucous membranes. Thus, any change in the rate of absorption or excre-

tion occurring with their use must be attributed to a local chemical or mechanical action.

### RESULTS

For an analysis of data in terms of therapeutic effectiveness, the bactericidal activity *in vitro* must be correlated *with* clinical or *in vivo* results. The average minimal effective level at which most gram-positive pathogens are killed faster than they multiply, or the concentrations at which these organisms fail to grow in culture, is 0.04 (0.039) unit of penicillin per c.c. of serum. For purposes of analysis, therefore, we elected to call this the "minimum therapeutic level." This, and higher levels, we have called "positive"; levels less than 0.04 unit per c.c. of serum we have called "negative."

Following aerosolization of penicillin in each diluent, serum levels were evaluated according to the above criteria. The overall effectiveness of a diluent was judged by the following determinations. First, by the number of sera at or exceeding 0.04 unit per c.c. throughout the entire two hours;

CHART I

Diluent	Physiologic Saline	Neosynephrin (1%)	Epinephrine (1%)	Triethylene Glycol (100%)	Chlorophyll (100%)	Pantopaque (100%)
No. of sera tested	36	35	33	33	27	26
Total percentage of positive sera*	69	66	33	18	44	11
Percentage of sera still positive at the end of two hours	25	45	9	9	0	11
Percentage of sera exceeding minimum therapeutic level	39	29	9	9	22	0

\* 0.04 unit or more.

this is expressed as the *total percentage of positive sera* for each vehicle. Second, by the ability of any particular diluent to affect absorption so that blood levels are positive for a longer period of time; this is reflected in the *percentage of sera still positive at the end of two hours*. Third, by the *percentage of sera whose penicillin activity exceeds the minimum therapeutic level* (i.e. more than 0.04 unit per c.c. of serum). Determination of the latter is important since the "minimum therapeutic level" is insufficient for complete bactericidal activity against many strains of susceptible organisms. Diluents which will so affect absorption that levels in a higher range result, must, therefore, be considered particularly effective. A summary of each aerosolized diluent analyzed according to these criteria is given in chart 1. Neosynephrin is a potent bronchovasoconstrictor with poor bronchodilator properties; epinephrine has less vasoconstrictor properties but is a

## CHART II

Tabulation of Blood Levels and Urinary Excretion Following the Inhalation of 100,000 Units of Crystalline Penicillin Potassium (C.S.C.) in Various Diluents in Normal Males

Hours After Dose	Penicillin, units per c.c. serum				Number of Sera Tested	Per Cent Positive Sera*	Urinary Excretion (Averages)
	<0.04	0.04	0.08	0.16			
Physiologic Saline							
$\frac{1}{2}$	1	4	5	2	12	92%	
1	1	5	6		12	92%	3,053
2	9	2	1		12	25%	922
24							574
Total	11	11	12	2	36	69%	4,549
Neosynephrin 1%							
$\frac{1}{2}$	2	4	5	1	12	83%	
1	4	4	4		12	66%	2,807
2	6	5			11	45%	1,526
24							195
Total	12	13	9	1	35	66%	4,528
Racemic Epinephrine 2.25%							
$\frac{1}{2}$	5	4	2		11	55%	
1	7	3	1		11	36%	1,235
2	10	1			11	09%	999
24							302
Total	22	8	3		33	33%	2,536
Triethylene Glycol (100%)							
$\frac{1}{2}$	8	2	1		11	27%	
1	9	1	1		11	18%	911
2	10		1		11	09%	602
24							371
Total	27	3	3		33	18%	1,844
Chloresium (100%)							
$\frac{1}{2}$		4	5		9	100%	
1	6	2	1		9	33%	630
2	9				9	0%	282
24							73
Total	15	6	6		27	44%	985
Pantopaque							
$\frac{1}{2}$	7	1			8	12%	
1	8	1			9	11%	446
2	8	1			9	11%	573
24							317
Total	23	3			26	11%	1,336

\* 0.04 unit or more.

powerful bronchodilator. One per cent neosynephrin and 2.5 per cent racemic epinephrine (Vaponefrin, analogous to 1.5 per cent U.S.P. epinephrine) were used as diluents. The effects on absorption of these two drugs as contrasted to saline were reflected in the blood levels (chart 2 and figure 1).

The total percentage of positive sera with saline (69 per cent) and neosynephrin (66 per cent) are essentially the same; whereas, only 33 per cent

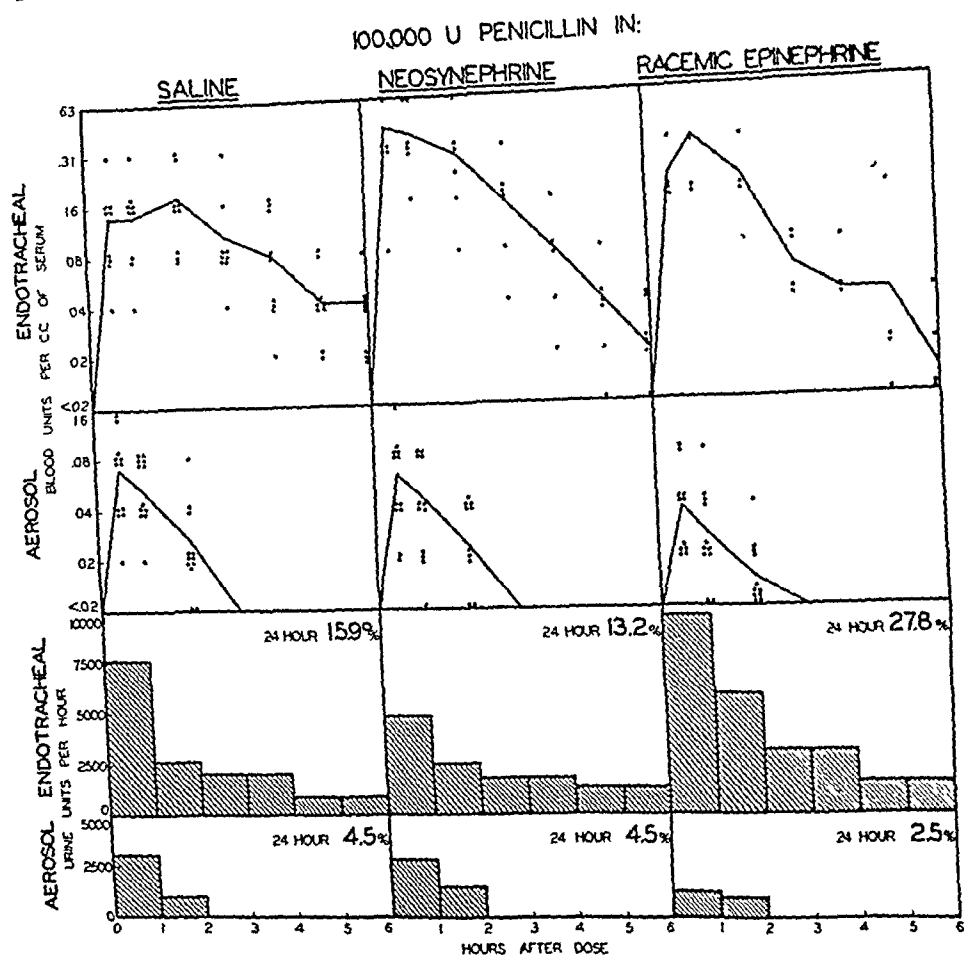


FIG. 1. Blood level curves and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by intratracheal and aerosol routes of administration in various diluents.

positive sera were obtained with racemic epinephrine (chart 1). The differences in the percentage of sera still positive at the end of two hours demonstrate the vasoconstricting action of neosynephrin on the absorption of penicillin; 45 per cent of the two-hour sera were positive as compared to 25 per cent with saline and only 9 per cent with epinephrine. The percentage of sera exceeding the minimum therapeutic level follows much the same pattern: with saline, 39 per cent, with neosynephrin, 29 per cent; and with epinephrine, 9 per cent. Total urinary excretions were consistent with the blood



levels; epinephrine, which gave the lowest blood levels, also gave the lowest urinary excretion.

Triethylene glycol, Pantopaque and chlorophyll were chosen as diluents for various reasons. Glycol vapors have been employed for air disinfection for many years.<sup>7, 8</sup> Singer et al.<sup>9</sup> demonstrated the delaying action of propylene glycol on the absorption of injected penicillin. Chlorophyll (Chloresium)\* was used in the form of a purified water-soluble derivative. It has been used extensively in the local treatment of traumatic and thermal wounds because of its deodorizing and antibacterial properties.<sup>10, 11</sup> The healing action of chlorophyll derivatives has been attributed to their glyco-

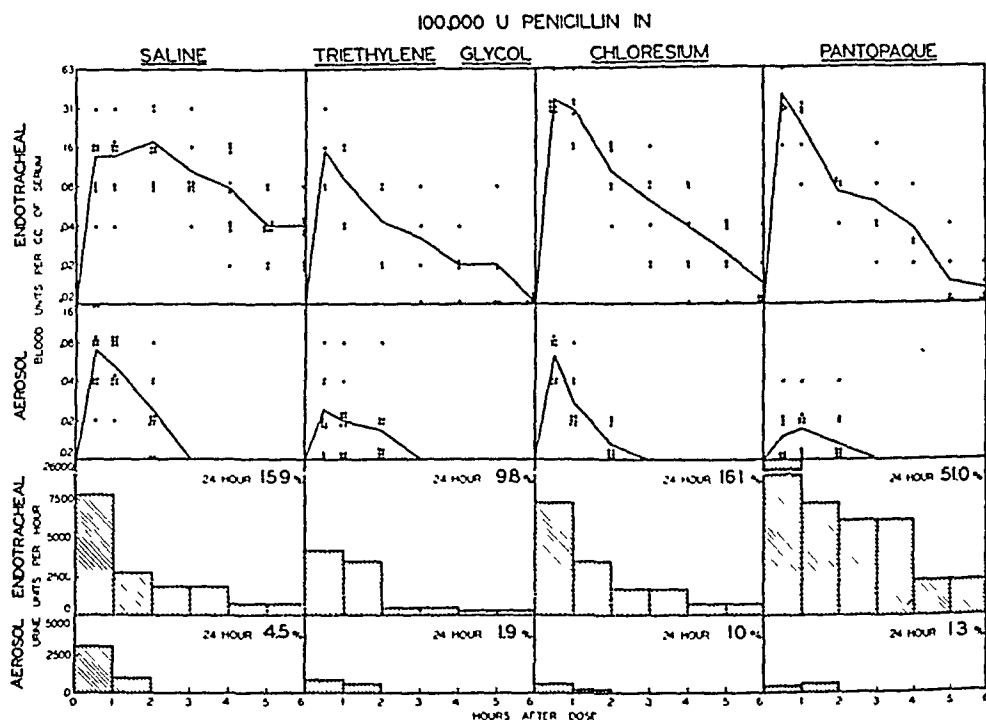


FIG. 2. Blood level curves and urinary excretion following the administration of 100,000 units of crystalline penicillin G potassium by intratracheal and aerosol routes of administration in various diluents.

lytic, oxygenating and other enzymic activities. We felt that such a substance might have a favorable action in suppurative disease of the lung. Its effect on penicillin absorption and excretion, when aerosolized as a diluent of the latter, was therefore investigated. Pantopaque, a mixture of ethyl esters of isomeric iodophenylundecylic acids, is an absorbable oil-type contrast medium of low viscosity, ordinarily used for myelography. Romansky<sup>12</sup> suggested a lipiodol-penicillin suspension for management of suppurative lung conditions. However, we felt that repeated injections of such a slowly eliminated, heavy oil would be undesirable in such diseases. A thinner, more easily eliminated iodized oil was considered more appro-

\* Chloresium, Rystan Co.

appropriate for intrapulmonary use. Since triethylene glycol and Pantopaque are relatively viscid and not easily aerosolized by the conventional nebulizer, a special Vaponefrin nebulizer, dispensing a larger particle size, was used.

These diluents, whose effect on absorption and excretion of penicillin is of a chemical or mechanical action, have a marked effect on the serum levels (chart 2 and figure 2). The blood levels and total urinary excretion were consistently lower than those obtained with physiologic saline. The *total percentage of positive sera* (chart 1) using triethylene glycol (18 per cent) or Pantopaque (11 per cent) compare unfavorably with that of saline (69 per cent); chlorophyll produced a somewhat higher number of sera in the therapeutic range (44 per cent). The *percentage of sera positive at the end of two hours* and the *percentage of sera whose penicillin activity exceeded the minimum therapeutic level* also did not compare favorably to that of saline when these diluents were used.

#### INTRATRACHEAL ADMINISTRATION

Direct instillation into the trachea should yield accurate data on the manner in which diluents affect absorption of penicillin from the tracheo-bronchial tree. With aerosolization, losses occur at the apparatus, into the air and in the mouth. We have shown elsewhere that only 35 per cent of an aerosolized substance actually reaches the lung. Exact quantitative evaluation is therefore difficult. In contrast, no losses occur with intratracheal administration unless the injected substance causes enough chemical irritation to produce cough and expectoration in spite of topical anesthesia.

We, therefore, elected to inject directly into the trachea the same diluents previously used by the aerosol route. Penicillin assay of bloods and urines following this type of administration were tabulated (chart 3) and correlated with the aerosol data (figures 1 and 2).

The results following the use of neosynephrin, epinephrine and saline as penicillin vehicles, by both aerosol and intratracheal routes, are compared in figure 1. Neosynephrin 1:100 was used for aerosolization but was diluted to 1:1,000 for intratracheal injection; racemic epinephrine (analogous to 1.5 per cent U.S.P. epinephrine) was employed for inhalation; and epinephrine for direct instillation was diluted to a 1:10,000 concentration because marked side reactions occurred with higher concentrations. Despite such low dilutions, these substances exerted a profound effect on the blood levels and urinary excretion of penicillin when injected endotracheally.

Certain striking facts are partially obscured by the logarithmic ordinates of our graphs. Actually, the average blood level at one-half hour following neosynephrin (0.43 unit) was exactly three times that obtained when saline was the diluent (0.14 unit). The ratio was maintained fairly closely at one hour and less so at two hours; at four hours, the average levels were the same (0.08 unit). The neosynephrin curve remained within the therapeutic range for five hours; the saline curve remained so for six hours. The

## CHART III

Blood Levels and Urinary Excretions of 100,000 Units of Crystalline Penicillin G Potassium (C.S.C.) in 10 c.c. of Various Diluents by Tracheal Catheter in Normal Males

	Blood							Urinary Excretion					
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.	Total
Physiologic Saline													
T. C.	.04	.04	.08	.08	.16	.04	.04	4,399	1,000	998	1,123	562	8,082
H. R.	.08	.08	.08	.08	.08	.08	.04	4,836	7,375	8,125	592	393	21,321
R. M.	.08	.16	.16	.08	.08	.08	.04	7,062	7,062	4,680	—	377	19,161
R. H.	.16	.08	.08	.08	.16	.04	.04	967	429	1,903	1,326	0	4,625
E. F.	.08	.16	.31	.31	.16	.04	.08	—	—	—	—	—	—
N. Mc.	.16	.16	.31	.04	.04	.02	.02	11,937	468	1,326	904	249	14,684
E. P.	.31	.31	.16	.16	.04	.04	.02	9,661	1,875	826	427	149	12,938
J. O.	.16	.16	.16	.08	.04	.04	.02	13,370	2,315	5,820	1,792	0	23,297
E. D.	.16	.16	.16	.08	.02	.02		12,000	1,250	5,250	4,650	200	23,350
Average	.14	.14	.17	.11	.08	.04	.04	7,654	2,597	3,866	1,546	241	15,932
Neosynephrin (1:1000)													
R. H.	.31	.31	.08	.04	.02	0	0	3,435	5,000	3,125	1,405	525	13,490
E. F.	.08	.16	.23	.16	.16	.08	.02	3,060	1,875	1,185	—	650	6,770
N. McL.	.31	.31	.31	.16	.08	.04	.04	2,500	312	624	10	0	3,446
E. P.	.31	.63	.31	.08	.08	.04	.04	—	2,250	6,250	2,500	187	—
J. O.	1.25	.63	.16	.16	.04	.02	.02	5,370	3,125	.288	498	118	9,399
E. D.	.31	.31	.63	.31	.08	.04	.02	10,000	2,250	10,250	7,870	2,500	32,870
Average	.43	.39	.29	.15	.08	.05	.02	4,873	2,468	3,620	2,456	663	13,196
Epinephrine (1:10,000)													
J. O'D.	.16	.16	.16	.08	.08	.16	.04	1,638	9,500	7,500	6,562	2,250	27,450
J. S.	.31	.63	.08	.04	.04	0	0	13,500	2,375	3,876	515	6,825	27,091
T. A.	.16	.16	.31	.04	.02	.02	0	10,750	6,250	10,750	2,313	1,575	31,638
H. D.	.16	.31	.16	.08	.04	.02	.02	12,250	5,000	2,813	2,563	2,275	24,901
Average	.20	.32	.18	.06	.05	.05	.02	9,555	5,781	6,235	2,988	3,206	27,770
Triethylene Glycol (100%)													
E. F.	.08	.04	.02	.02	.02	.08	0	2,180	5,820	545	545	150	8,940
N. McL.	.31	.16	.08	.04	.02	0	0	3,040	5,060	900	530	120	9,650
E. P.	.16	.16	.08	.08	.04	.02	0	7,500	2,620	3,000	2,370	334	15,824
J. O.	.08	.04	.02	0	0	0	0	3,930	734	331	0	0	4,995
Average	.16	.10	.05	.04	.02	.02	0	4,162	3,559	1,189	861	151	9,852
Chloresium (100%)													
R. H.	.31	.31	.08	.02	0	0	0	15,000	6,860	5,310	1,150	50	28,370
N. McL.	.31	.16	.08	.04	.02	.02	.02	9,480	2,730	3,120	2,960	370	18,660
E. W.	.31	.31	.16	.08	.08	.04	0	2,620	625	4,620	2,090	140	10,095
E. P.	.31	.31	.16	.08	.04	.04	0	3,060	3,060	3,740	1,385	1,338	12,583
J. O.	.31	.16	.04	.02	.02	.02	0	6,570	2,805	1,482	2,340	140	13,337
E. D.	.63	.63	.16	.16	.08	.04	.04	6,500	4,370	2,500	0	0	13,370
Average	.36	.31	.11	.07	.04	.03	.01	7,205	3,408	3,462	1,654	340	16,069

CHART III—Continued

	Blood							Urinary Excretion					
	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	1 hr.	2 hr.	4 hr.	6 hr.	24 hr.	Total
Pantopaque													
P. M.	.63	.31	.08	.16	.08	.04	.02	33,250	8,500	17,500	15,375	89	74,714
P. F.	.31	.31	.08	.04	.03	.02	.01	27,000	10,500	16,500	402	200	54,602
A. H.	.16	.08	.04	.02	—	0	0	—	—	—	—	—	—
J. F.	.31	.16	.08	.04	.02	0	0	33,750	5,000	8,375	2,122	162	49,409
J. O'D.	.31	.31	.08	.08	.03	0	0	12,500	4,992	6,718	800	200	25,210
Average	.34	.23	.07	.07	.04	.01	.01	26,625	7,248	12,273	4,675	162	50,983
Human Serum													
J. C.	.23	.08	.08	.04	.02	0	0	4,000	4,000	2,500	2,500	115	12,115
R. C.	.16	.16	.16	.08	.02	.02	0	6,240	6,240	12,500	12,500	438	37,918
R. W.	.16	.08	.08	.06	.06	.04	.04	12,500	12,500	12,500	6,240	1,575	45,315
J. H.	.31	.63	.31	.31	.16	.08	.04	18,740	25,000	12,500	1,560	2,850	60,650
Average	.22	.24	.16	.12	.07	.04	.02	10,370	11,935	10,000	5,700	1,245	39,250

penicillin blood curve with endotracheal epinephrine lay between the neosynephrin and saline curves and remained within the therapeutic range for five hours.

The amount of penicillin excreted in the urine following endotracheal administration with these diluents varied. Average recovery in the urine after the use of epinephrine was greater at each time interval than with either neosynephrin or saline and the total average excretion was approximately twice that obtained with either of the other vehicles. Although the total average excretion with neosynephrin was slightly lower than with saline, most of this difference occurred in the first hour; after the fourth hour, recovery with neosynephrine was moderately higher than with saline.

The blood level curves following aerosolization of penicillin in each of these diluents have been fully discussed above. Correlation with the endotracheal data just presented discloses fair consistency. However, the lower recovery in the urine following aerosolization with epinephrine is inconsistent with the comparatively high recovery following intratracheal injection with this same substance.

The absorption and excretion of penicillin when injected endotracheally with triethylene glycol, chlorophyll or Pantopaque is compared to saline (figure 2). A micronized crystalline penicillin G potassium powder with an average particle size of less than two micra was mixed with Pantopaque when this substance was studied intratracheally. Unlike all other substances which we injected into the trachea, chlorophyll and especially triethylene glycol were markedly irritating in 100 per cent concentrations and varying amounts of penicillin were lost because of resultant cough and expectoration. It is noteworthy that instillation of Pantopaque did not lead to cough.

serum is not effective as a depot for penicillin. The average recovery of 39,250 units in the urine (chart 3) was comparatively high.

## DISCUSSION

The effect of several diluents on the absorption of penicillin from the lung has been studied by aerosol and intratracheal routes of administration. Bloods and urines were assayed for penicillin activity and the results compared to those obtained following the administration of penicillin in saline via the same routes.

Penicillin in 10 c.c. neosynephrin (1:1000) by intratracheal injection gave initial levels three times as high as corresponding levels with saline. In addition to these initially high levels, a therapeutic blood level was maintained for five hours. The accepted bronchovasoconstrictor action of this drug should tend, theoretically, to slow down adsorption into the blood stream rather than hasten it. The results with aerosol penicillin-neosynephrin closely resembled those with aerosol penicillin-saline; a greater percentage of positive sera at the end of two hours with aerosolized neosynephrin demonstrated delayed absorption. Neosynephrin aerosol appeared to produce a more uniform and diffuse shrinkage of the bronchial mucous membrane than when administered by the intratracheal route. Neosynephrin, as a bronchovasoconstrictor, afforded marked symptomatic relief when obstruction of the bronchi was due to swollen, edematous mucous membrane. It is more stable than epinephrine, and its sympathicomimetic effects, which are slower in onset but more lasting, are attended with less untoward reactions. Furthermore, its tendency to retard the absorption of aerosolized penicillin, thereby aiding greater local concentrations, is highly desirable.

Epinephrine is more potent as a bronchodilator than as a bronchovasoconstrictor. When this drug was injected intratracheally in a 1:10,000 dilution with penicillin, the blood level curve lay between the saline and neosynephrin curve. The blood levels remained therapeutically effective for five hours. The much higher fractional and total recovery of penicillin in the urine than that obtained with either neosynephrin or saline was striking. When aerosolized with penicillin, the blood levels and recovery in the urine were less than those obtained with either neosynephrin or saline. The vasoconstrictor action of epinephrine, however, was still in evidence. Since epinephrine primarily constricts arterioles rather than capillaries, such low blood levels might indicate that normally the arterioles are an important route of absorption. The comparatively high urinary excretion, however, does not bear this out; a delayed absorption would be reflected in a lower excretion inasmuch as the body inactivation or detoxification of penicillin would have more time to progress.

Side effects, including cough, were notably absent when neosynephrin and epinephrine, in the described dosages, were aerosolized or injected intratracheally. There did not appear to be any contraindication to their com-

bination with penicillin when the clinical picture warranted the use of either to combat bronchospasm, mucosal swelling or both. On the contrary, definite beneficial local effects, in addition to their pharmacologic actions, appeared to be exerted.

Triethylene glycol did not seem to hold any particular advantage as a diluent by either the aerosol or intratracheal routes. As it was too viscid for easy aerosolization with the conventional nebulizer, the blood levels following its administration with a special large particle size nebulizer were disappointing. Moreover, by intratracheal route, it was extremely irritating to the tracheobronchial tree. Low blood levels and urinary excretion may be argued as indicating local retention in the lung; in fact, studies in which triethylene glycol was tagged with radioactive substances indicated a greater local retention of penicillin when combined with this diluent than with other substances.<sup>17</sup> A slowing of absorption would, of course, result in low early blood levels but, conversely, blood samples at later intervals would continue to show penicillin activity, albeit still in the lower ranges. Following intratracheal injection, all individual six-hour levels and one-half of the five-hour levels were zero. Following aerosolization, only one of the 11 sera tested at the end of two hours was within a therapeutic range. With neither route, therefore, could delayed absorption be ascribed to a glycol-penicillin combination. Other reports have described the glycols as enhancing the bactericidal action of penicillin when combined with the latter. In fact, a bactericidal action of glycol alone in the blood stream has been claimed.<sup>18</sup> However, these conclusions were based on a bacteriological technic which used *B. subtilis* as a test organism; normal blood has been shown to exhibit antibodies in various titers for these organisms.<sup>19</sup> A false impression of bactericidal activity in the serum may, therefore, result when *B. subtilis* is used as the test organism. In addition to our routine studies, we repeated the above mentioned study<sup>18</sup> where 100,000 units of penicillin was aerosolized in a mixture of 19 c.c. of triethylene glycol and 1 c.c. of glycerol. We employed the O.E.M. head-tent. A double assay of several blood and urine specimens was done using both streptococcus No. 98 and *B. subtilis* as test organisms. As we could not demonstrate any penicillin in either the blood or urine, we were, therefore, unable to detect either delay in absorption or potentiation of the bactericidal action of penicillin when it was combined with glycol.

Initial blood levels, with chlorophyll as a diluent, were higher than the saline levels, especially when administered intratracheally. With both routes, however, levels were not maintained within a therapeutic range for as long a time as with saline. Chlorophyll, in 25 per cent dilution, was not irritating to the tracheobronchial tree but full strength solution, when given intratracheally, did cause cough despite topical anesthesia. However, chlorophyll may be of practical value when the bacterial flora includes anaerobic organisms. Because it causes more rapid absorption of penicillin, its administration would have to be repeated at shorter time intervals.

In a previous study,<sup>1</sup> it was pointed out that routine intratracheal administration of penicillin was usually not practical for several reasons. At the same time, it was felt that this method of treatment could be utilized in conjunction with bronchoscopy, bronchography and other procedures requiring endotracheal instillation. Therefore, the effect of iodized oil on penicillin absorption was of great interest. Pantopaque is much less viscous than lipiodol or iodochlorol. It was used because of certain practical considerations which favor its clinical use in place of the heavier, more difficultly eliminated oils. It was felt that a light oil such as Pantopaque would still be heavy enough to sterilize or cleanse cylindrical and saccular dilatations of the bronchi which have become clogged with thick mucus. Its greater specific gravity would encourage a "floating" or displacement of such plugs which could then be more easily expectorated. Combining penicillin with a physical therapeutic agent of this type would probably be advantageous. Since the iodine of Pantopaque (approximately 30 per cent) is present in firm organic combination, it was not to be expected that the iodine present would act as an expectorant. However, some loosening of the secretions may occur. The blood level curve with intratracheal Pantopaque was maintained in the therapeutic range for four hours. In comparison to every other diluent studied, the urinary excretion of more than 50 per cent was astounding. Since both the diluent (Pantopaque) and the penicillin preparation (micronized powder) were different from the other substances studied via the same route, some factor, either in the combination or in either of the individual substances, could possibly be the cause of this unusual recovery in the urine. Unlike other diluents which formed a true solution, penicillin powder was merely suspended in Pantopaque. Further studies are planned with micronized penicillin by this and the aerosol route and also with radioopaque substances by the intratracheal route.

Localization of both penicillin G and K has been demonstrated in the kidney, lung and liver to an extent not explained by the blood or extracellular fluid content of these organs.<sup>20</sup> Penicillin G is localized more extensively in the lung and kidney; penicillin K, more extensively in the liver. Pantopaque, human serum and epinephrine may possibly enhance this natural localization of penicillin G in the lung and kidney. This mechanism may offer a possible explanation for the markedly higher urinary excretion with average or below average blood level curves obtained with these diluents when injected endotracheally.

#### SUMMARY

1. The effect of several diluents on the absorption of penicillin from the lungs has been studied by aerosol and intratracheal routes of administration. Assay of penicillin activity in the serum and recovery in the urine was compared to results obtained following the administration of penicillin in saline by the same routes.

2. Both neosynephrin and epinephrine, constrictors of the bronchial mucous membrane, caused higher initial blood levels than corresponding results with saline when injected intratracheally. Levels were sustained within a therapeutic range for five hours. The bronchovasoconstricting action of neosynephrin was more in evidence when aerosolized with penicillin.

3. When the aerosolization of either or both of these substances with penicillin was indicated clinically, their local pharmacologic action on the tracheobronchial tree favorably affected absorption of penicillin. Irritation or side reactions were not present with either route of administration.

4. Triethylene glycol was too viscid for easy aerosolization and too irritating, at full strength, for intratracheal injection. Neither a bactericidal action of its own, enhancement of penicillin activity in the serum nor a delaying action on the absorption of penicillin could be demonstrated.

5. Chlorophyll caused more rapid absorption of penicillin but levels were not maintained within a therapeutic range for as great a length of time as with saline. One hundred per cent solution was irritating to the tracheobronchial tree, but a 25 per cent solution was well tolerated by intratracheal instillation. Chlorophyll with penicillin, in the treatment of mixed gram positive and negative bacterial flora, should be repeated frequently in order to maintain high local antibiotic activity. Chlorophyll (endotracheal) should be of definite value for the management of anaerobic bacterial bronchopulmonary infections.

6. Intratracheal injection of emulsions of penicillin in the lighter iodized oils in the treatment of bronchopulmonary suppurative disease is discussed. The cleansing action of the oil at the site of localized collections of pus and the displacement or "floating" of mucous plugs would permit more effective local action of penicillin injected at the same time.

7. Human serum as a vehicle did not greatly alter the absorption of penicillin from the lung.

#### BIBLIOGRAPHY

1. GAENSLER, E. A., BEAKEY, J. F., and SEGAL, M. S.: Pharmacodynamics of pulmonary absorption in man. I. Aerosol and intratracheal penicillin, *Ann. Int. Med.*, 1949, xxxi, 582.
2. GRAESER, J. B., and ROWE, A. H.: Inhalation of epinephrine for the relief of asthmatic symptoms, *Jr. Allergy*, 1935, vi, 415.
3. SEGAL, M. S., and BEAKEY, J. F.: The use of 1-(3'-4'-dihydroxyphenyl)-2-isopropylaminoethanol for the management of bronchial asthma. A preliminary report, *Bull. New England Med. Center*, 1947, ix, 62.
4. RAMMELKAMP, C. H.: A method of determining the concentration of penicillin in body fluids and exudates, *Proc. Soc. Exper. Biol. and Med.*, 1942, ii, 95.
5. MEAKINS, J. C., SMITH, F., and GOLD, M. A.: A comparative study of some commercial preparations of oral penicillin, *Canad. Med. Assoc. Jr.*, 1946, lv, 97.
6. GOODMAN, L., and GILMAN, A.: *The pharmacological basis of therapeutics*, 1941, pg. 405, Macmillan Co., New York.
7. HARRIS, T. N., and STOKES, J., JR.: Summary of a three year study of the clinical application of the disinfection of air by glycol vapors, *Am. Jr. Med. Sci.*, 1945, ccix, 152.



8. BIGG, E., JENNINGS, B. H., and OLSON, F. C. W.: Epidemiologic observations on the use of glycol vapors for air sterilization, *Am. Jr. Pub. Health*, 1945, xxxv, 788.
9. SINGER, F. L., WARRES, H. L., and RITKIN, I.: Penicillin in propylene glycol: a preliminary report, *Jr. Urol.*, 1946, lv, 138.
10. BOEHRINGER, M. L.: Action of chlorophyll on healing of wounds, *Praxis*, 1943, xxxii, 791.
11. SMITH, L. W., and LIVINGSTON, A. E.: Wound healing: an experimental study of water-soluble chlorophyll derivatives in conjunction with various antibacterial agents, *Am. Jr. Surg., New Series*, 1945, lxxvii, 30.
12. ROMANSKY, M. S., DUGAN, D. J., and RITTMAN, G. E.: Penicillin in iodized oil for instillation into the lungs, *Science*, 1945, cii, 255.
13. COURTICE, F. C., and PHIPPS, P. J.: The absorption of fluids from the lungs, *Jr. Physiol.*, 1946, cv, 186.
14. DRINKER, C. K., and HARDENBERGH, E.: Absorption from the pulmonary alveoli, *Jr. Exper. Med.*, 1947, lxxxvi, 7.
15. INGRAHAM, F., and GAENSLER, E. A.: Unpublished data, 1944.
16. TOMPSETT, R., SCHULTZ, S., and McDERMOTT, W.: The relation of protein binding to the pharmacology and antibacterial activity of penicillins X, G, dehydro E, and K, *Jr. Bact.*, 1947, liii, 581.
17. TALBOT, T. R., JR., QUIMBY, E. H., and BARACH, A. L.: A method of determining the site of retention of aerosols within the respiratory tract of man by the use of radioactive sodium, *Am. Jr. Med. Sci.*, 1947, ccxiv, 585.
18. PRIGAL, S. J., MCGAVACK, T. H., SPEER, F. D., and HARRIS, R.: Aerosol penicillin, *Jr. Am. Med. Assoc.*, 1947, cxxxiv, 932.
19. BRIGGS, C. H., BRONSTEIN, B., HIRSHFIELD, J. W., and PILLING, M. A.: The presence in normal serum of inhibiting substances against *B. subtilis*, *Science*, 1946, ciii, 363.
20. RICHARDSON, A. P.: Studies on the pharmacology of penicillin G and K, *Proc. Am. Fed. Clin. Res.*, 1947, iii, 62.

# TREATMENT OF HEART AND KIDNEY DISEASE AND OF HYPERTENSIVE AND ARTERIO- SCLEROTIC VASCULAR DISEASE WITH THE RICE DIET \*

By WALTER KEMPNER, M.D., *Durham, N. C.*†

THE treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet is either ineffective or dangerous, unless it is done under rigidly controlled conditions. Ineffective, because small or "minimal" additions to the diet may spoil the entire therapeutic result; dangerous, because a strict observance of the diet may lead to a deficiency of vitally important elements unless care is taken that the equilibrium between intake and loss of these substances is maintained. For both reasons, therefore, continuous supervision, over a long period of time, including constant checks of blood and urine chemistry, is essential.

Rigidly controlled conditions are likewise indispensable for the evaluation of the therapeutic results. Claims of positive or negative results based on nothing but blood pressure readings for four to eight weeks before and after treatment and not substantiated by heart films, electrocardiograms, eye-ground photographs and chemical findings do not contribute much to the solution of this problem.

The same authors who a few years ago insisted that the restriction of salt, protein or fat is unwarranted in the treatment of hypertensive and arteriosclerotic vascular disease, now admit the importance of these dietary restrictions. No matter what the value of the restriction of sodium or of chloride or of protein or of cholesterol may be, the fact is: The rice diet contains less sodium and less chloride than any other diet which has been devised to reduce the sodium and chloride intake. It contains less protein than any other diet which has been devised to reduce the protein intake. It contains less cholesterol and other fat than any other diet which has been devised to reduce the cholesterol and fat intake.

The rice diet contains in 2,000 calories less than 5 gm. of fat and about 20 gm. of protein derived from rice and fruit and less than 200 mg. of chloride and 150 mg. of sodium. This does not mean that the patient's caloric intake is restricted to 2,000 calories; it varies according to whether weight gain or weight loss, protein increase or protein decrease is desirable in the individual patient.

\*Read at the Thirtieth Annual Session, American College of Physicians, New York, N. Y., March 30, 1949.

From the Department of Medicine, Duke University School of Medicine.

† This work was supported by grants from the A. H. Hanes Research Fund, the Life Insurance Medical Research Fund, and the U. S. Public Health Service.

Figure 1 shows a comparison of the most important constituents of the urine on a normal diet and after at least two months on the rice diet. The total nitrogen content has decreased from 15.0 gm. to 2.3 gm.; the urea nitrogen from 12.0 gm. to 1.1 gm.; the uric acid nitrogen from 0.3 gm. to 0.08 gm.; the total creatine nitrogen from 0.6 gm. to 0.4 gm.; the ammonia nitrogen from 0.6 gm. to 0.1 gm.; the sodium from 4.0 gm. to 0.01 gm. The potassium has increased from 2.0 gm. to 3.0 gm. The chloride has decreased from 7.0 gm. to 0.1 gm.; the inorganic phosphate from 1.0 gm. to 0.3 gm. The chloride has decreased from 7.0 gm. to 0.1 gm.; the inorganic phosphate from 1.0 gm.

URINARY EXCRETION (GM IN 24 HR) ON "NORMAL" DIET AND ON RICE DIET (FOR 2 MONTHS OR MORE)

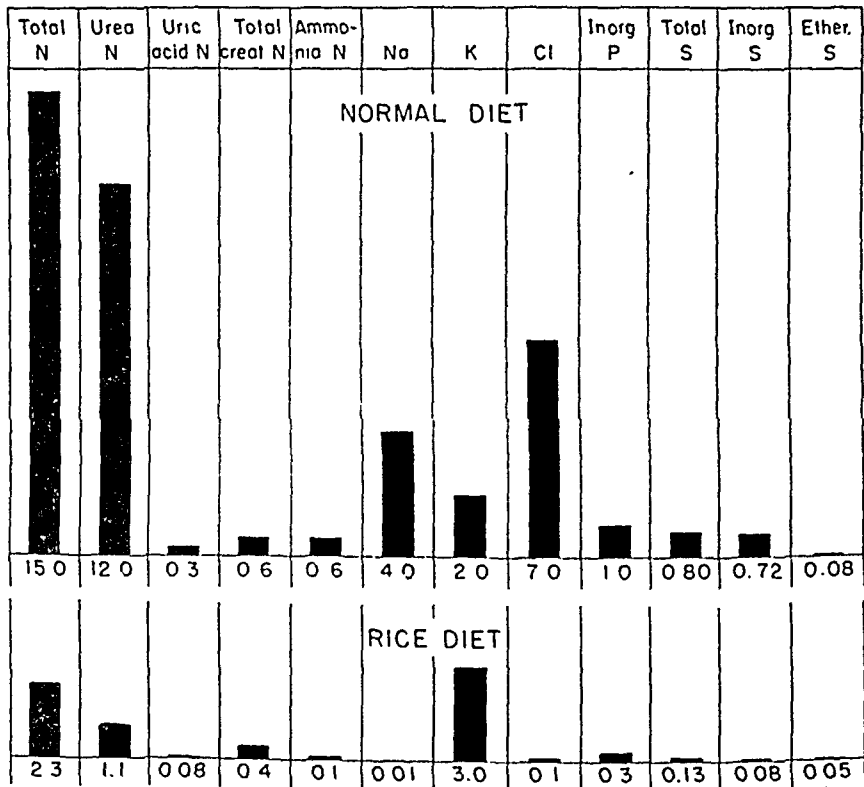


FIG. 1.

to 0.3 gm.; the total sulfate from 0.80 gm. to 0.13 gm.; the inorganic sulfate from 0.72 gm. to 0.08 gm.; the ethereal sulfate from 0.08 gm. to 0.05 gm.

The figures show that the marked decrease in the intake of nitrogen, sodium, chloride, sulfate, etc., on the strict rice diet, is followed by a marked decrease in the excretion of these substances by the kidney. Any deviation from these figures—except in rare cases—indicates that this particular diet has not been followed strictly for any length of time, and also in what way—either deliberately or unintentionally—it has been changed.

A small amount of nitrogen is also excreted through the bowels; a comparison of the daily nitrogen intake with the daily nitrogen output by stool

and urine shows that the nitrogen equilibrium on the rice diet can easily be maintained (table 1).

There are other indications that, because of the protein sparing action of the carbohydrates, the protein part of the rice diet is adequate and that there is no lack of essential amino acids; e.g., the fact that the production of hemoglobin is normal and that anemia does not develop. Also the fact that blood urea and non-protein nitrogen decrease on the rice diet whereas in starvation and in protein deficiency the body uses its own protein and the non-protein nitrogen and the urea nitrogen in the blood increase.

Other differences between starvation and the rice diet are: in starvation, the serum calcium is decreased, on the rice diet unchanged. In starvation, the plasma protein and the A/G ratio are decreased, on the rice diet unchanged or, if low before, often become normal. In starvation, the blood sugar is decreased, on the rice diet unchanged. In starvation, the carbohydrate tolerance is decreased, on the rice diet increased. In starvation, the serum phospholipids are increased, on the rice diet decreased. In starvation, the CO<sub>2</sub> combining power is decreased, on the rice diet increased. In star-

TABLE I  
Nitrogen Balance After 60 Days on Rice Diet, gm.N in 24 hrs.  
(Averages of 4 consecutive days)

	Intake	Output		Balance
		urine	stool	
W. C.		2.61	1.81	
m., 59	4.66	4.42		+0.24

vation, the blood volume remains unchanged or—in relation to body weight—increases; on the rice diet, according to Murphy's determinations, it decreases. In starvation, the interstitial fluid remains unchanged or increases; on the rice diet it decreases. (N. B., there is no simple relationship between volume changes and clinical course.) In starvation, the excretion of total creatine bodies in the urine is unchanged; on the rice diet it is decreased. In starvation, the excretion of creatine, ammonia and organic acids is increased, on the rice diet decreased. In starvation, the excretion of total sulfate and inorganic phosphate is decreased, on the rice diet markedly decreased (table 2).

In 490 patients with hypertensive vascular disease and an initial non-protein nitrogen of 20 to 45 mg. per 100 c.c. of blood, there was an average decrease of the non-protein nitrogen from 33 to 28 mg. per 100 c.c. of blood after an average period of 98 days. There was an average decrease of the urea nitrogen from 14 to 8 mg. (table 3). These figures are also interesting in another connection: a decreased salt intake in the diet with ensuing hypochloremia is usually followed by an increase in the blood urea nitrogen,

TABLE II  
Chemical Differences between Starvation and Rice Diet

	Starvation	Rice Diet
Blood (or serum)		
Hemoglobin, RBC	Decreased	Unchanged
Calcium	Decreased	Unchanged
Total protein	Decreased	Unchanged (returned to normal if decreased before)
A:G ratio	Decreased	Unchanged
NPN	Increased	Decreased
Urea N	Increased	Decreased
Sugar	Decreased	Unchanged
Carbohydrate tolerance	Decreased	Increased
Phospholipid	Increased	Decreased
Alkali Reserve	Decreased	Increased
Blood volume	Unchanged	Decreased
Interstitial fluid	Unchanged or increased	Decreased
Nitrogen balance	Negative	In equilibrium
Urine		
Total nitrogen	Decreased	Markedly decreased
Urea N	Decreased	Markedly decreased
Creatinine + creatine	Unchanged	Decreased
Creatine	Increased	Decreased
Ammonia N	Increased	Decreased
Organic acids	Increased	Decreased
Total sulfate	Decreased	Markedly decreased
Inorganic phosphate	Decreased	Markedly decreased

and consequently by an increase in the total non-protein nitrogen. On the rice diet the salt is limited and the serum chlorides do decrease to a lower level. However, the restriction of the protein in the diet outweighs the effect of salt restriction and usually protects against the azotemia.

It might, perhaps, be well to talk less about the quantity of protein. The important thing is not how much protein is eaten, but how much of what kind of protein. There is actually no such thing as "protein." Proteins differ from each other in regard both to the type and the relative proportions of the various amino acids of which they are composed. They also differ in regard to rate and degree of assimilation. These differences as far as the patient is concerned are indicated by what is termed the biological value of

TABLE III  
Average NPN and Urea-N of 490 Patients with Hypertensive Vascular Disease  
(Initial NPN 20 to 45 mg. per 100 c.c. Blood)

	Before	After 98 (Average) Days of
	Rice Diet	
NPN (mg./100 c.c. Blood)	33	28
Urea-N (mg./100 c.c. Blood)	14	8

various proteins. It is of no advantage to the patient to receive a large amount of protein with a low biological value which cannot be properly utilized. Moreover, certain patients should use protein only for essential purposes and not merely to supply calories which can just as well be supplied by the oxidation and fermentation of carbohydrates.

The same considerations which apply to protein and essential amino acids are also valid with regard to fat and essential fatty acids. The absolute fat content of rice for instance is small, but the proportion of linoleic acid, an essential fatty acid, is high.

One of the lipids which is supposed to have an important rôle in the development of vascular disease is cholesterol. A high cholesterol concentration in the serum is frequently found in arteriosclerosis, coronary artery disease, exudative vascular retinopathy, hypertensive vascular disease, as well as in diseases of the lens and vitreous body, in uncontrolled diabetes mellitus and in the nephrotic stage of nephritis.

TABLE IV  
Total Serum Cholesterol of 511 Patients with Hypertensive Vascular Disease

	Before	After	Average Period of Rice Diet (Days)
	Rice Diet		
148 Patients with initial concentration below 220 mg. per 100 c.c. serum	186	171	120
363 Patients with initial concentration above 219 mg. per 100 c.c. serum	279	205	102

An easy way to produce arteriosclerosis is by feeding cholesterol to rabbits. In dogs it is not so easy. The aging process in the human species seems to be a change from the dog state to the rabbit state. The cholesterol metabolism becomes inadequate and the average serum cholesterol concentration of men of 50 is higher than that of men of 20 who have an identical cholesterol intake. However, if a 20 year old man has a disease which causes a hypercholesterolemia, the same sequelae may occur as in the 50 year old man. The literature describes cases of arteriosclerosis in diabetic children as young as one year.

We have examined the effect of the rice diet on the total serum cholesterol of 511 patients with hypertensive vascular disease (table 4). In 148 patients (29 per cent) who started the rice diet with a normal serum cholesterol, the average decrease was 15 mg. per 100 c.c. of serum after an average period of 120 days. In 363 patients (71 per cent) who had a hypercholesterolemia before the rice diet, the average decrease was 74 mg. after an average period of 102 days.

These figures show that, no matter from what fatty or non-fatty substances the cholesterol in the body is derived, and by what mechanism a high

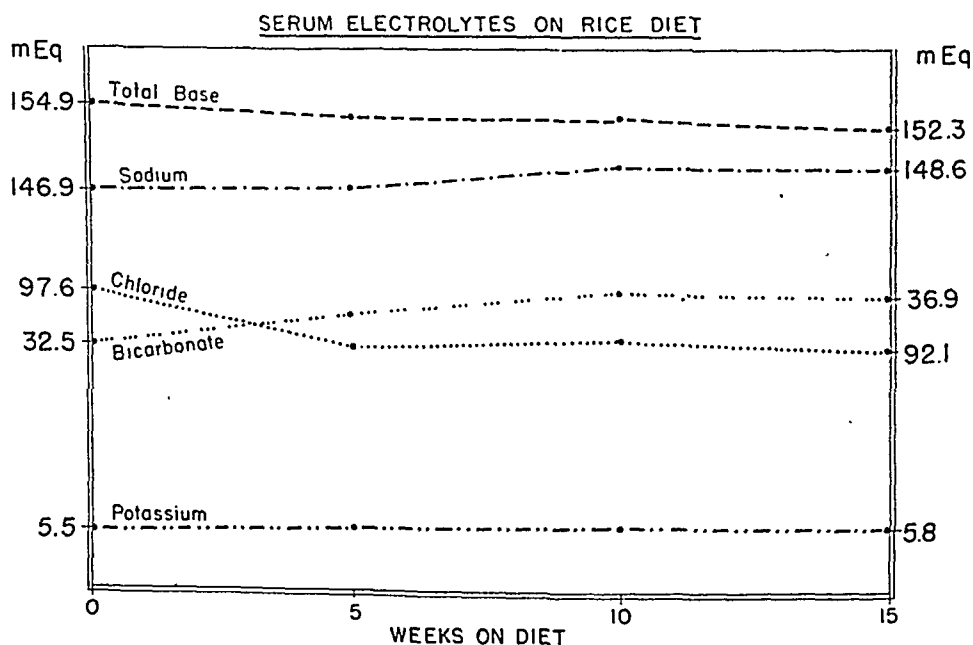
TABLE V

Total and Free Cholesterol in Serum of 118 Patients with Hypertensive Vascular Disease  
(Initial total cholesterol 220-463 mg. in 100 c.c. serum)

	Before	After 56 Days (Average) on
	Rice Diet	
Total cholesterol (mg. in 100 c.c. serum)	288	217
Free cholesterol (mg. in 100 c.c. serum)	82.2	65.7
Ratio Free: Total cholesterol (%)	27.8	30.5

serum cholesterol concentration is produced, the serum cholesterol need not necessarily remain high, as has been assumed, but can be decreased by the rice diet.

As Starke has found, both cholesterol fractions, the free and the esterified cholesterol, decrease on the rice diet (table 5). One hundred and eighteen patients with an initial hypercholesterolemia of 220 to 463 mg. per 100 c.c. of serum were examined. The total cholesterol decreased in 113 of the 118 patients. The total cholesterol did not decrease in five of the 118 patients. In the entire group of 118 patients, there was a decrease of the total cholesterol from 288 to 217 (average), of the free cholesterol from 82.2 to 65.7 (average), of the esterified cholesterol from 205.8 to 151.3 (average). In



Average values of 12 patients with hypertensive vascular disease  
(without evidence of renal involvement)

FIG. 2.

TABLE VI

Lipid Phosphorus in Serum of 42 Patients with Hypertensive Vascular Disease  
(Mg. lipid P in 100 c.c. serum)

Before	After 78 Days (Average) on
Rice Diet	
9.91	8.87

ACIDS AND BASES IN URINE  
*NORMAL*

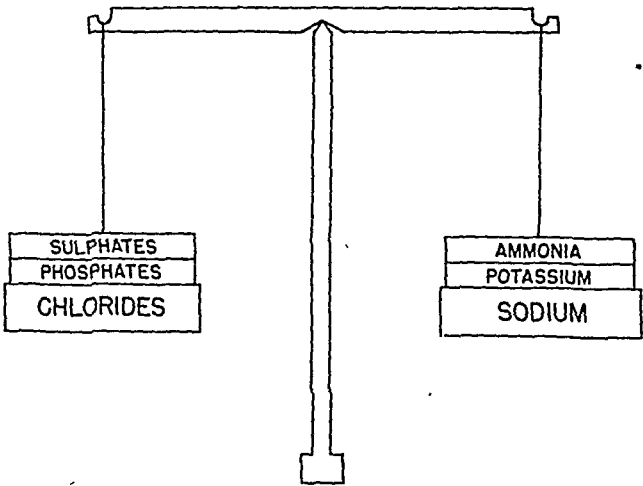


FIG. 3.

ACIDS AND BASES IN URINE  
*RENAL INSUFFICIENCY*

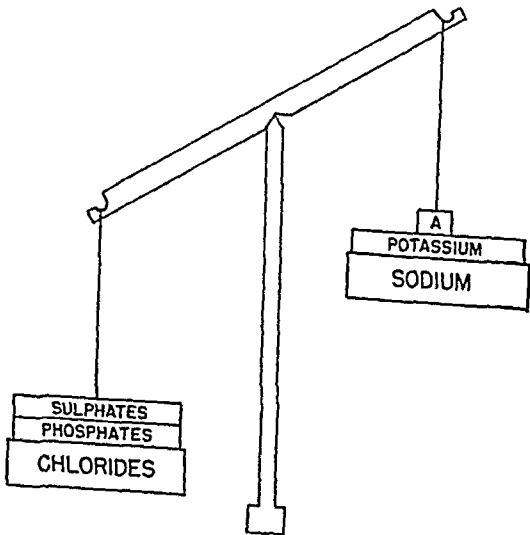


FIG. 4.



42 patients with hypertensive vascular disease, the serum phospholipids were determined. There was a decrease from 9.9 to 8.9 mg. lipid phosphorus per 100 c.c. (table 6).

Figure 2 shows the changes in concentration of sodium, chloride, potassium, bicarbonate, and total base in the serum of 12 patients on the rice diet. After an average period of 15 weeks, the serum chloride showed a definite decrease, the serum bicarbonate a definite increase; the serum sodium, potassium and total base remained relatively constant.

Another change in the mineral metabolism of patients on the rice diet is in the urinary excretion of inorganic sulfates and inorganic phosphates. The inorganic sulfate excretion decreases by 82 per cent, the inorganic phosphate excretion decreases by 62 per cent.

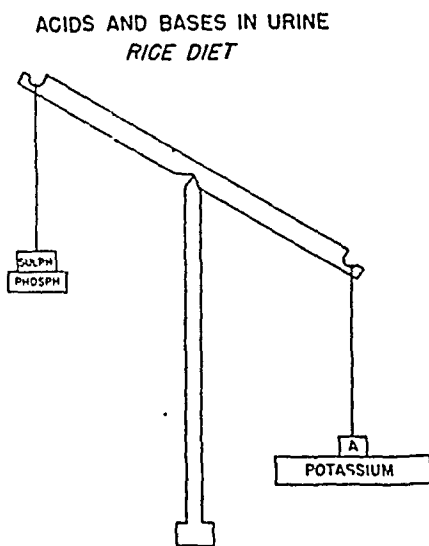


FIG. 5.

These findings are interesting for two reasons: Since phosphates and sulfates are derived mostly from protein, the decreased excretion of phosphorus and sulfur shows again that on the rice diet no endogenous protein is being broken down. Secondly, the sulfate and phosphate metabolism is important because of the acid-base balance. The scales (figure 3) represent this balance in the normal urine. The acids are on one side, the bases on the other side. In kidney insufficiency, the scale goes down on the acid side (figure 4). The kidney has lost one of its main metabolic functions: It is no longer able to form ammonia. On the rice diet, the urine chloride concentration is decreased. This does not affect the acid-base equilibrium because it is counterbalanced by the decrease in the sodium excretion. However, the potassium concentration on the base side is increased, and the sulfate and phosphate concentration on the acid side is decreased, so that even with an insufficient ammonia formation the urine becomes alkaline (figure 5).

Now let me turn from the chemical changes to the clinical changes produced by the rice diet. I will avoid long-winded statistics as much as possible and will try to discuss the main problems by showing you some typical cases as examples of what can be achieved in the individual patient.

The first case is that of a 13 year old school girl in the nephrotic stage of chronic nephritis. It is an example of the disappearance of marked generalized *renal* edema and hypoproteinemia on the rice diet. Early in Jan-

B.H. (f. 13) Nephrotic Stage of Chronic Glomerulonephritis

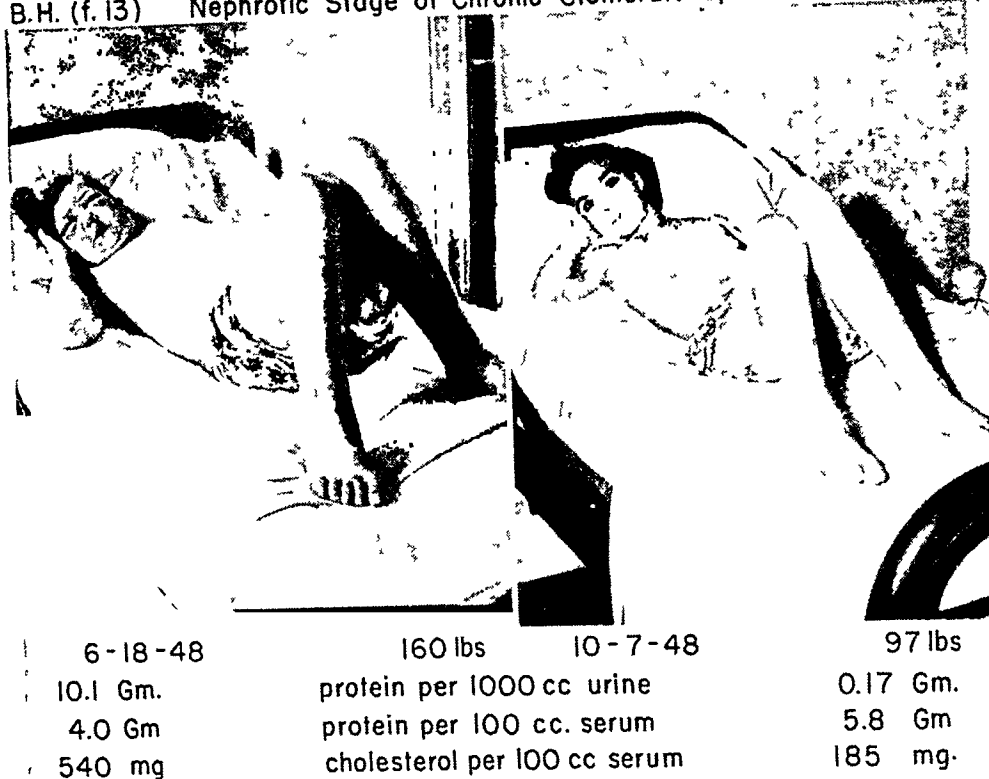


FIG. 6.

uary, 1948, this girl developed swelling of the lower extremities after a sore throat. She was treated by bed rest, salt-poor diet (for part of the time, high protein diet), and penicillin. In February, 1948, massive anasarca developed; a paracentesis was done which resulted in a weight loss of 22 pounds. Later, because of marked dyspnea, a thoracocentesis was necessary and one quart of fluid was removed from the right pleural cavity. During June, the facial edema which had been present since January became worse and the general edema and ascites increased. When the oliguria became serious, the patient was referred to us. The rice diet was started on June 18, 1948. No further paracentesis or thoracocentesis was done. The albuminuria decreased from 10.1 gm. per liter (average during the first 20 days on the rice diet) to 0.17 gm. (average after 111 to 131 days of rice diet). The

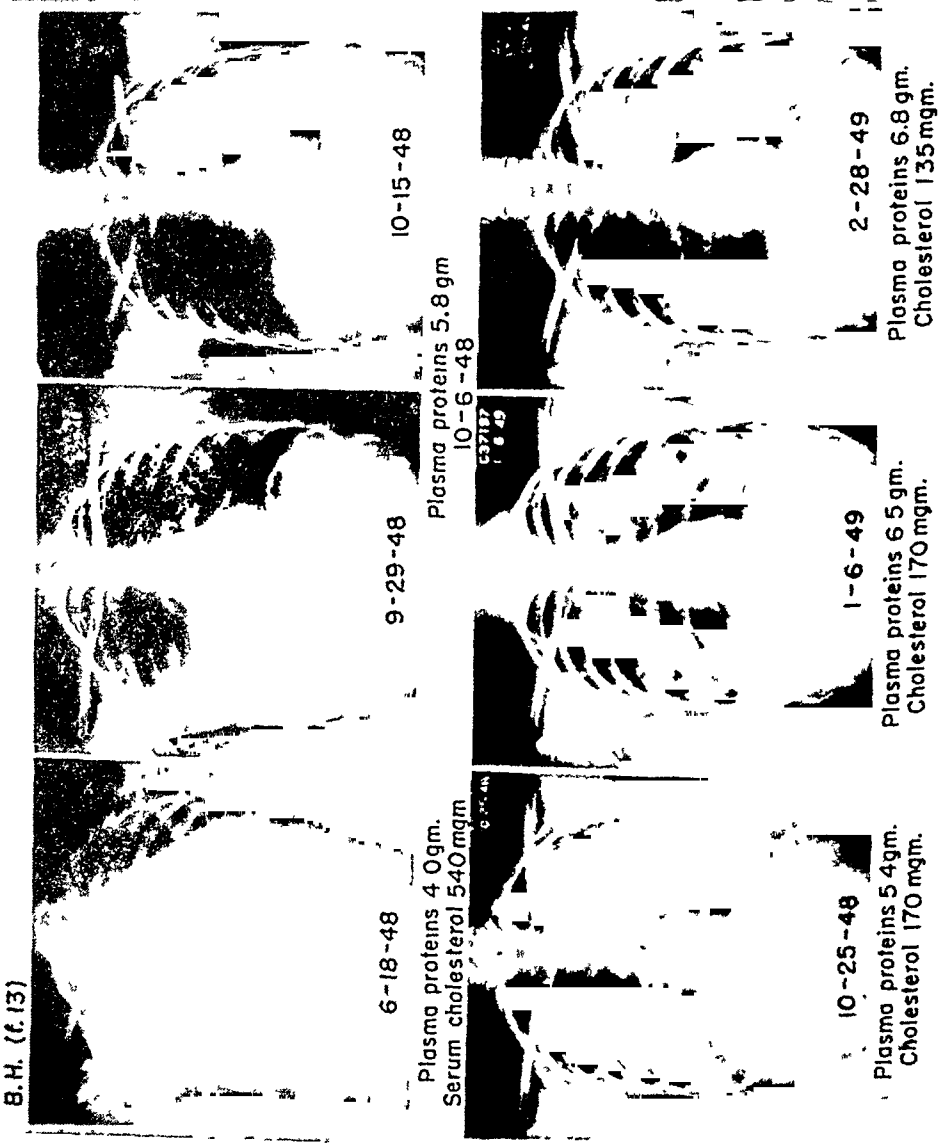


FIG. 7.

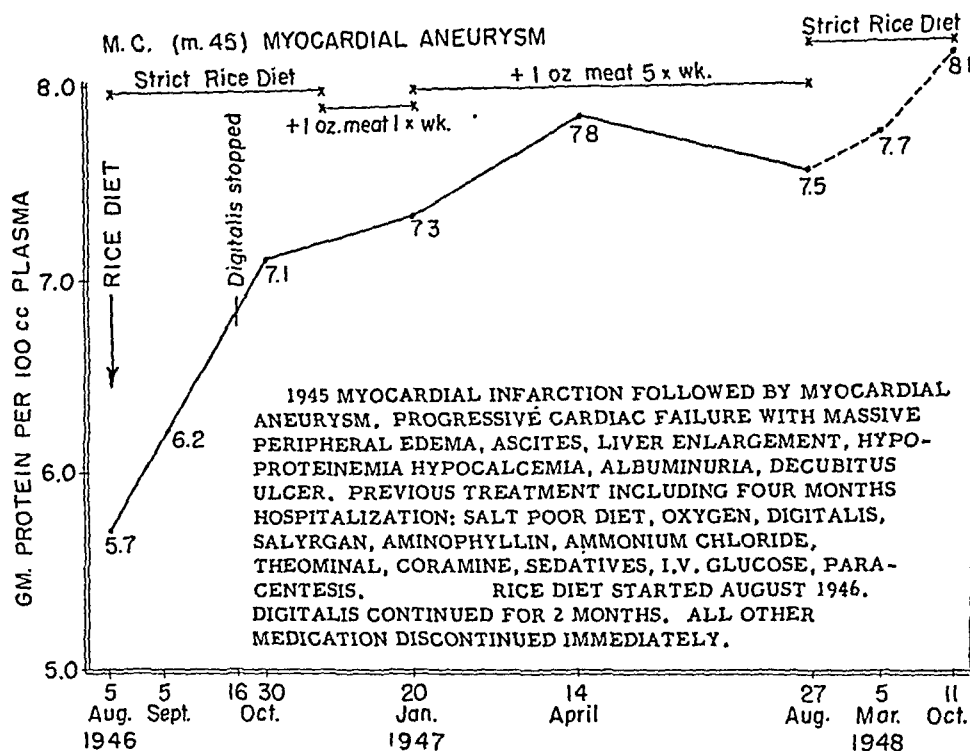


FIG. 8.

plasma protein increased from 4.0 gm. to 5.8 gm. The cholesterol decreased during this period from 540 mg. per 100 c.c. of serum to 185 mg. There was a total weight loss of 63 pounds in 15 weeks with gradual disappearance of ascites and pleural effusion. After eight months on the rice diet, the

M.C. (m.45)

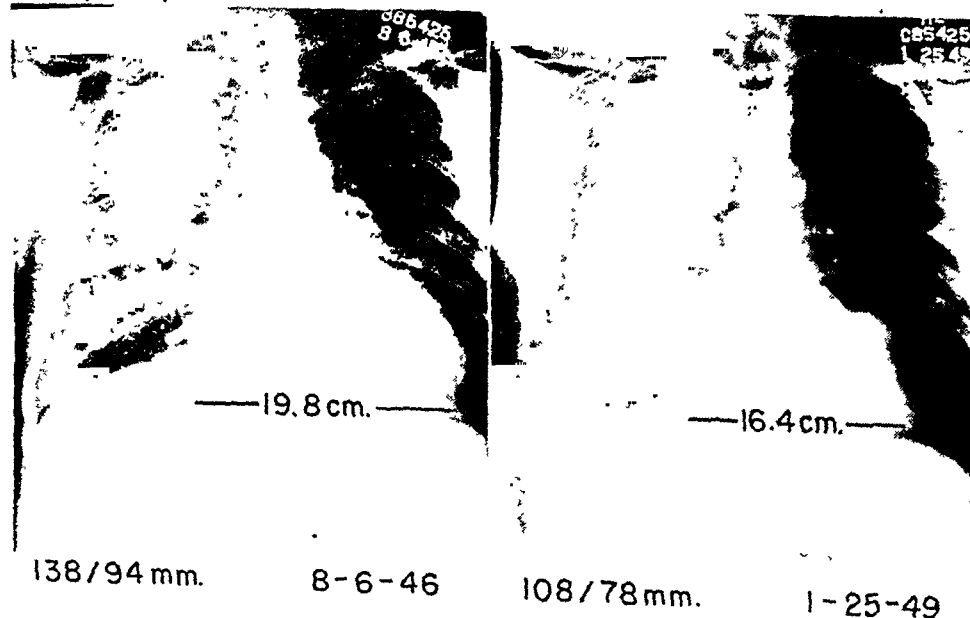


FIG. 9.

plasma protein had increased from 4.0 to 6.8 gm., the cholesterol had decreased from 540 to 135 mg. per 100 c.c. of serum (figures 6 and 7).

Figure 8 shows an example of the effect of the rice diet on the plasma protein of a patient with massive *cardiac* edema and ascites. This patient was a 45 year old man who had had a myocardial infarction in 1945. This

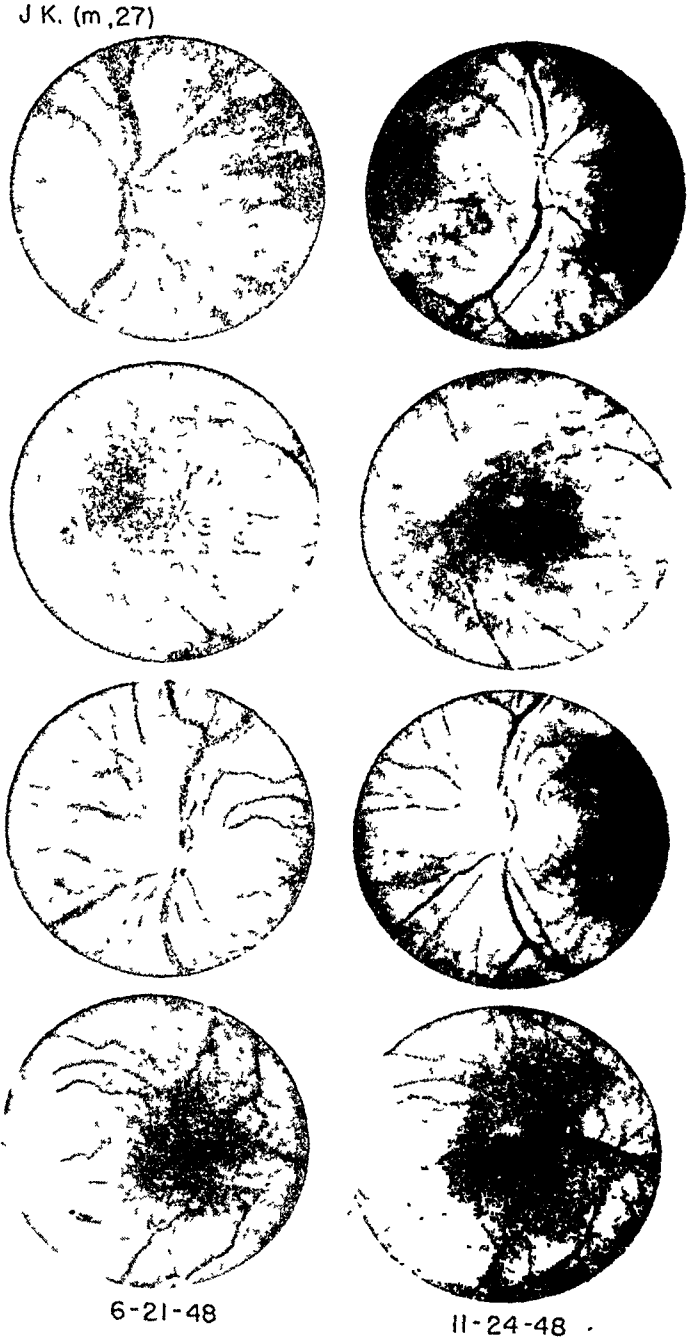


FIG. 10.

was followed by a myocardial aneurysm, progressive cardiac failure with massive peripheral edema, ascites, liver enlargement, hypoproteinemia, hypocalcemia, albuminuria, and decubitus ulcers. Previous treatment, including four months' hospitalization, consisted of salt-free diet, oxygen, digitalis, salyrgan, aminophyllin, ammonium chloride, theominal, coramine, sedatives; i.v. glucose; paracentesis. The rice diet was started August 7, 1946, and was strictly followed; a paracentesis was done August 13. Digitalis was continued for two months, but all other medications were discontinued immediately. There was a loss of weight (edema) of 50 pounds in 10 weeks. Up to the present time (two and one-half years later), the patient has received no medication; he is up and around and completely asymptomatic. The plasma proteins have increased from 5.7 gm. per 100 c.c. to 8.2 gm.

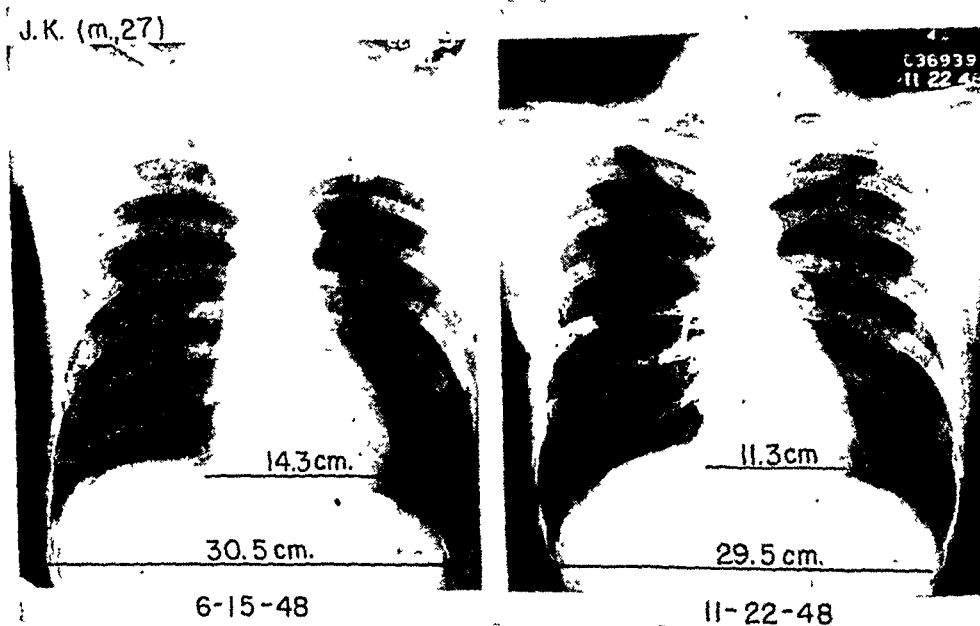


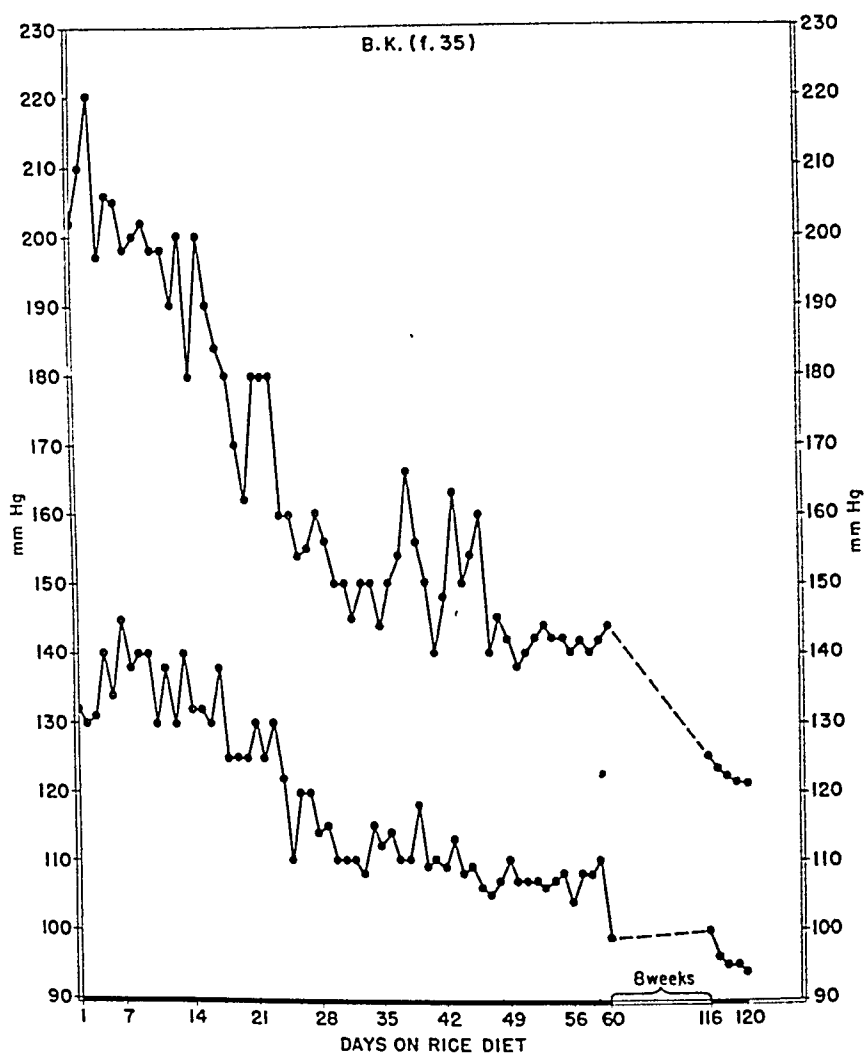
FIG. 11.

The heart is considerably smaller and the aneurysm of the posterior lateral wall of the left ventricle is now clearly visible in the A-P view (figure 9).

The patient, whose eyeground photographs and chest films are shown in figures 10 and 11, is an example of the effect of the rice diet on retinopathy and cardiac enlargement in chronic glomerulonephritis.

The patient was a 27 year old man who two years before admission to Duke Hospital, while in the Navy, had scarlet fever and acute glomerulonephritis, followed by chronic glomerulonephritis. He had been hospitalized for 16 months and treated with rest and various diets. During the month prior to admission, the patient had an exacerbation of his headache, noted blurring of vision and had a generalized convulsion, for which magnesium sulfate was given. At the start of the rice diet the blood pressure was 180

mm. of mercury systolic and 120 diastolic, the heart was enlarged, the vision considerably impaired, with bilateral marked papilledema, many hemorrhages and extensive exudates. The total phenolsulphonephthalein excretion in two hours was 7 per cent. The non-protein nitrogen was 90, the urea N 66.4 mg. per 100 c.c. of blood. The calcium was 7.8, the phosphorus 6.6, the



Reprinted from the *American Journal of Medicine*, 4, April, 1948.

FIG. 12.

cholesterol 350 mg. per 100 c.c. of serum. The serum chloride was 99.8 mEq. per liter.

After five months on the rice diet, the total PSP excretion in two hours was still only 10 per cent, but the NPN was 36, the urea N 15.8 mg. per 100 c.c. of blood. The calcium was 8.9, the phosphorus 5.1, the cholesterol 210 mg. per 100 c.c. of serum. The serum chloride was 88.2 mEq. per liter. The blood pressure was 137/99. The patient was asymptomatic; he had

regained his eyesight; papilledema, hemorrhages and most of the exudates had disappeared; the heart had decreased in size with a change in the transverse diameter of 27 per cent.

I have shown you some effects of the rice diet on edema, ascites, heart enlargement and retinopathy in patients with primary kidney disease. I will show you now some characteristic examples of the effect of the rice diet on hypertensive vascular disease without evidence of any primary renal disease. In more than 70 per cent of 777 patients most of whom were seriously ill and had failed to respond to other forms of treatment, the rice diet, given for periods of four to 1,150 days (average 92 days), has proved beneficial; that means that it has produced one or more of the following effects: decrease in the sum of systolic and diastolic blood pressure of at least

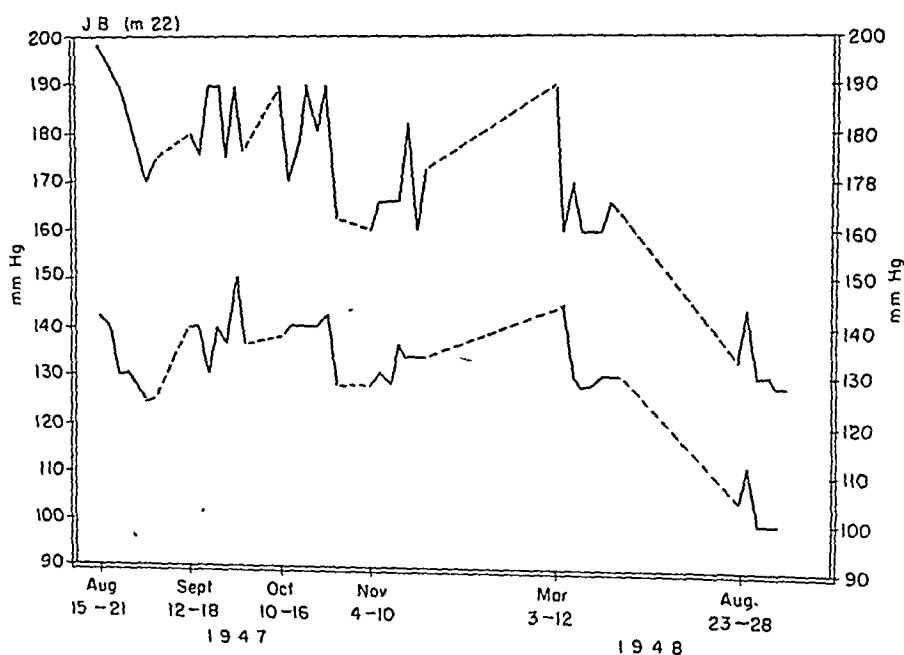


FIG. 13.

40 mm. Hg; reduction in heart size with change in the transverse diameter of 18 per cent or more; change in  $T_1$  from completely inverted to upright; disappearance of severe retinopathy.

I will begin with three typical cases of so-called benign essential hypertension without serious cardiac, renal or retinal complications.

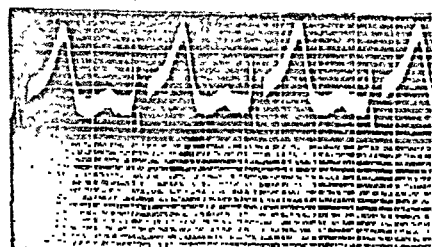
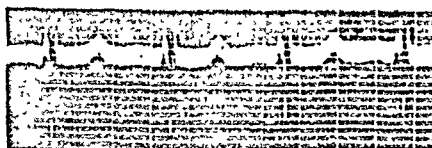
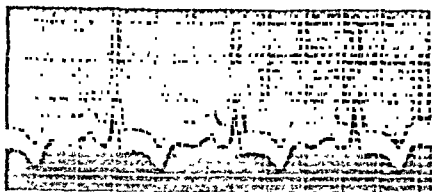
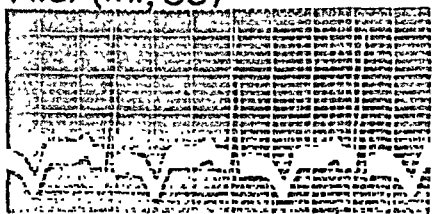
The first one is an example of a satisfactory response to the diet in about four months. It is the case of a 35 year old woman who had had hypertensive vascular disease for 11 years. There was no evidence of any renal excretory involvement. Of two brothers with hypertensive vascular disease, one had died of a stroke at the age of 37. For years, the patient did not feel up to par with increasing fatigue and exhaustion. There was a sensation of pressure and throbbing in the back of the head and in the eyes. From January to April, 1947, because of the appearance of retinal hemor-



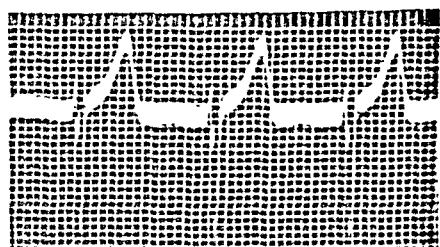
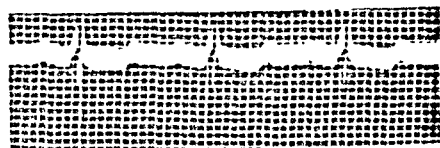
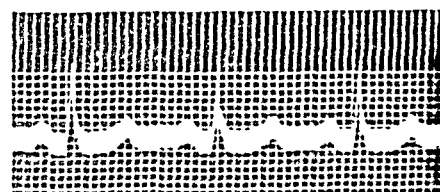
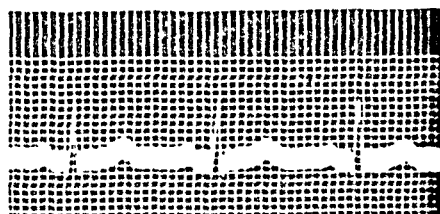
rhages, rutin, vitamin K and sedatives were given; all activities had been severely restricted.

The patient began the rice diet in April, 1947. All medication was discontinued. On the first day of the diet, the blood pressure was 202/132; after three weeks of the diet the blood pressure was almost as high as before: 180/132. After 120 days, the blood pressure was 122/95 (figure 12). It has remained at this level until the present time (two years) in spite of the

A.S. (m., 35)



6-4-46

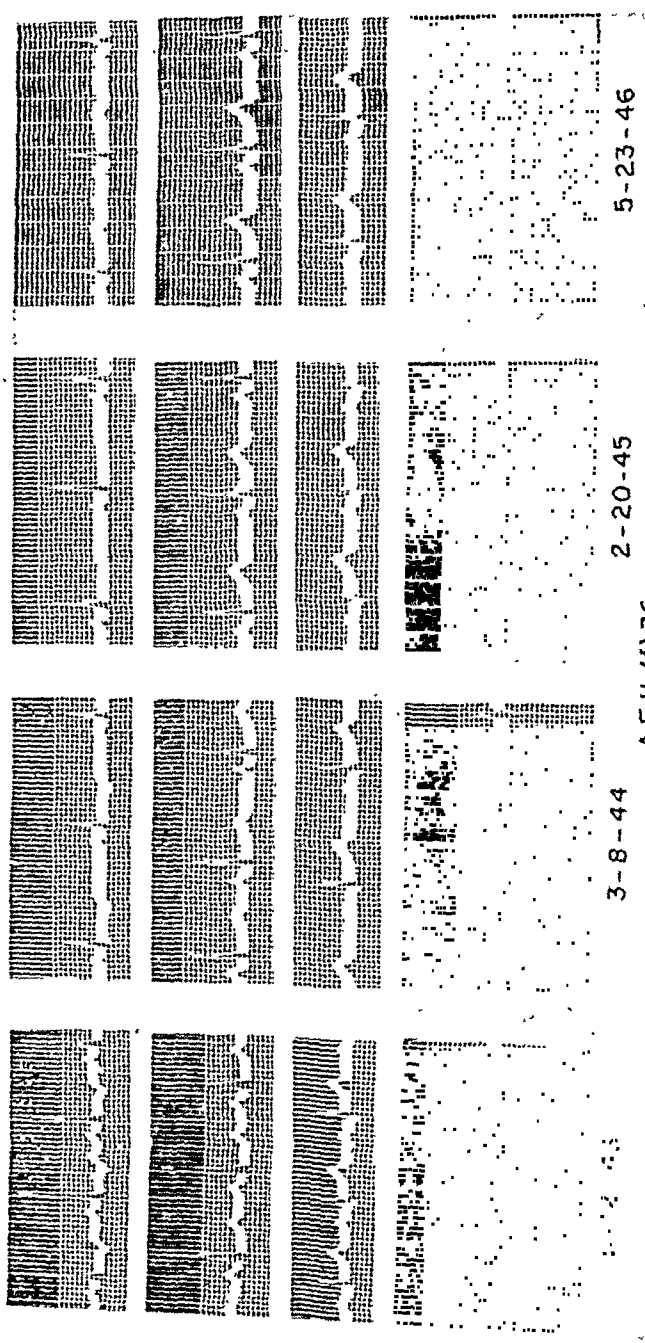


10-12-48

FIG. 14.

fact that two ounces of meat, one potato, 9 oz. of vegetables, one cup of coffee per day and 2 oz. of vegetable oil, 4 oz. of spaghetti per week, have been added to the diet. The patient has resumed her activities and is completely well.

The second case is an example of a rather slow response of hypertension to the diet. It is the case of a 22 year old man with benign essential hypertension without any history of kidney disease or evidence of renal excretory dysfunction. The patient had known about his hypertension for six months.



Reprinted from the *American Journal of Medicine*, 4, April, 1948.  
FIG. 15.

He was asymptomatic except for intense headaches. He was started on the rice diet in New York. Since the blood pressure did not change in seven and one-half weeks, he came to Durham. During August, September and October, 1947, while he was staying in Durham continuously, the blood pressure remained persistently at a level of 170 to 190 systolic and 130 to 145 diastolic; the headache, however, disappeared. When the patient returned for reexamination in November, 1947, and March, 1948, the blood pressure was as high as before. From June, 1948, on, i.e., 12 months after the rice diet was started, his physician in Alberta noticed that the blood pressure was decreasing. When the patient returned to us in August, 1948, after 14

TABLE VII  
Blood Pressure Response According to Length of Time of Treatment

	Number of Patients	Percentage	Average Period on Rice Diet (Days)
4-1150 Days			
Total	777		92
Blood pressure not improved	226*	29%	72
Blood pressure improved	551	71%	101
4-74 Days			
Total	392		37
Blood pressure not improved	151**	38.5%	32
Blood pressure improved	241	61.5%	40
75-1150 Days			
Total	385		149
Blood pressure not improved	75***	19.5%	153
Blood pressure improved	310	80.5%	148

\* Including 33 patients who died after 48 days (average).

\*\* Including 25 patients who died after 32 days (average).

\*\*\* Including 8 patients who died after 100 days (average).

months on the rice diet, the blood pressure was as low as 128/100 (figure 13).

The shortest time in which we have seen a marked blood pressure decrease on the rice diet was four days. The average time is about three to four months.

Table 7 shows the positive and negative results of treatment in 777 patients with hypertensive vascular disease who followed the rice diet for four to 1150 days (average 92 days). There was a definite decrease of the blood pressure level in 71 per cent of the total group. The average of this decrease was from 198/116 to 150/96 in 101 days. If one differentiates the results according to the length of time the patients have been following the

diet, the importance of the time factor becomes obvious: In 392 patients who followed the diet for four to 74 days (average 37 days), there was a definite lowering of the blood pressure in 62 per cent. In 385 patients who followed the diet for 75 to 1,150 days (average 149 days), there was a definite lowering of the blood pressure level in 81 per cent.

The third case with benign essential hypertension is an example of a satisfactory response to the diet in one month. It is the case of a man now 47 years old who was well until he was 37. In March, 1940, he was seen in the New York Hospital. The blood pressure was 165 to 200 systolic and 105 to 135 diastolic. A diagnosis of hypertensive vascular disease was

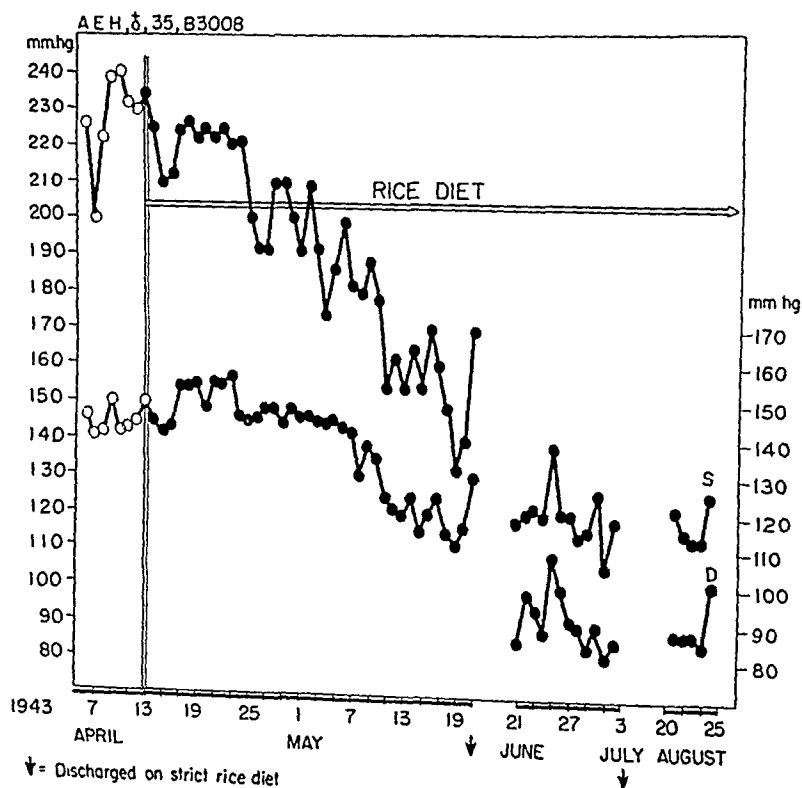
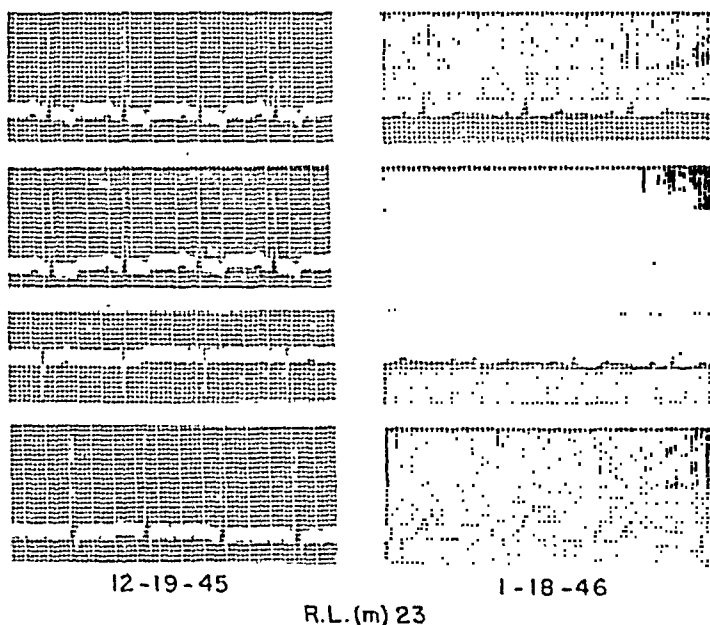


FIG. 16.

made. In January, 1941, he was seen in the Presbyterian Hospital. The blood pressure was found to be 200/140. One month later, the patient was seen in the Rockefeller Hospital with a blood pressure of 200/140. He was treated there by Dr. Henry Schroeder with tyrosinase until this had to be discontinued because of a severe shock-like reaction. As a matter of fact, this was the last patient whom Dr. Schroeder treated with tyrosinase. I like to show his record because Dr. Schroeder in the *American Journal of Medicine* in April of last year made the statement that the control periods preceding the rice diet might be too short to get an accurate base line for studying the effect of the diet. As is true for the majority of my patients, the base line for this patient was recorded by good observers not only over

a period of weeks or months but over a period of years. In this particular case, there are not only the figures of the New York and Presbyterian Hospitals but also those of Dr. Schroeder himself. After the tyrosinase treatment had failed, the patient went to Dr. Smithwick in Boston, where a lumbodorsal sympathectomy was done.

The sympathectomy did not help this patient. The blood pressure figures 14 months after the operation were even slightly higher than before. In 1945, the patient had a therapeutic trial with testosterone with no result. In March, 1945, when he came to us, he had tightness around the heart, headaches and swimming in the head. He had difficulty in walking and complained about a tendency to go toward the left and had at times run into



Reprinted from the *American Journal of Medicine*, 4, April, 1948.

FIG. 17.

walls. The blood pressure was 220/132. The average of daily blood pressure readings during 20 days while he was in the hospital on a 1,500 calorie diet was 197/129. No evidence of renal excretory dysfunction was found. PSP and urea clearance tests were normal. The rice diet was started on April 20, 1945. The blood pressure after one month of diet was normal and has remained normal to the present time. On February 24, 1949, it was 114/82. The diphasic  $T_1$  in the electrocardiogram reverted to normally upright in seven months, and has remained upright since. The heart became smaller in size with a change in the transverse diameter of 12 per cent. The patient who was a sick man when he came to us in 1945, is now—four years later—well and active.

Patients such as these three, with so-called benign essential hypertension

are frequently told not to be concerned about their disease, unless some complication develops.

I believe the most appropriate time for treatment is before the more incapacitating complications of the disease have developed (cardiac breakdown, cerebral accidents, loss of vision and renal insufficiency). However, I will show you some typical electrocardiograms, chest films and eyeground photographs, which will illustrate that hypertensive vascular disease can be compensated to a great extent even when critical complications are already present.

Figure 14 shows the reversion of an abnormal electrocardiographic pattern to normal in a 35 year old man with hypertensive vascular disease of

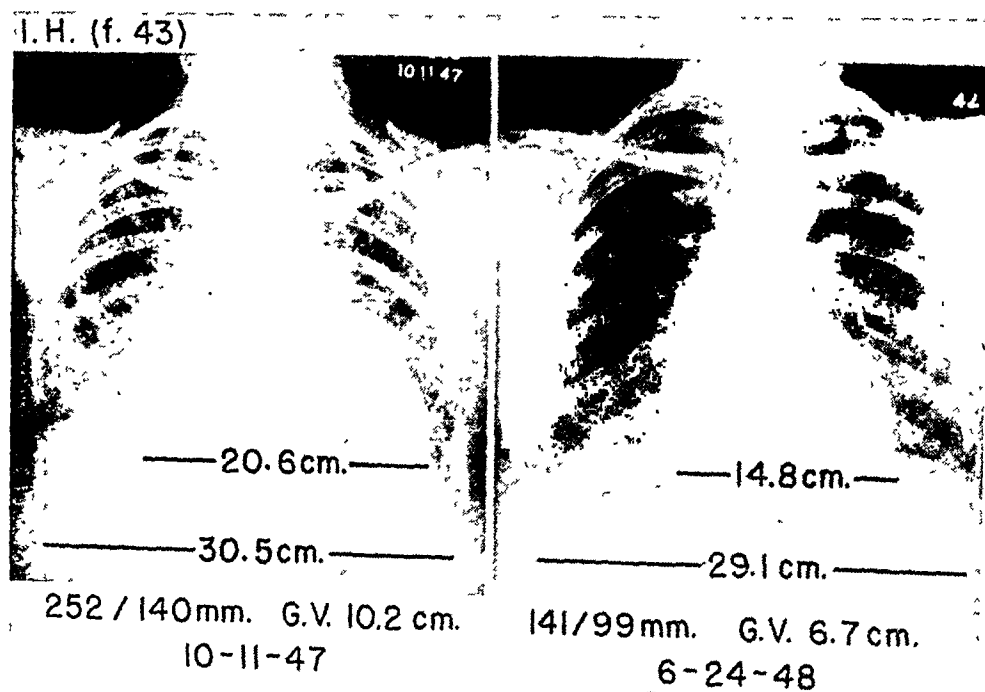


FIG. 18.

less than three years' duration. The change in the electrocardiogram is seen after 26 months on the rice diet. The blood pressure during this time decreased from an average of 205/122 to 150/103. Retinal hemorrhages and exudates disappeared. The deeply inverted  $T_1$  became upright; the electrical axis improved.

Figure 15 illustrates the time factor in the gradual improvement of  $T_1$ . The patient was a 35 or 36 year old woman. Hypertension was known to be present for about one year. In May, 1943,  $T_1$  was deeply inverted; in March, 1944,  $T_1$  was low inverted; in February, 1945, low upright; in May, 1946, normally upright. This case also shows that there is neither a simple relationship between blood pressure drop and  $T_1$  improvement nor between reduction in heart size and  $T_1$  improvement. The blood pressure decreased

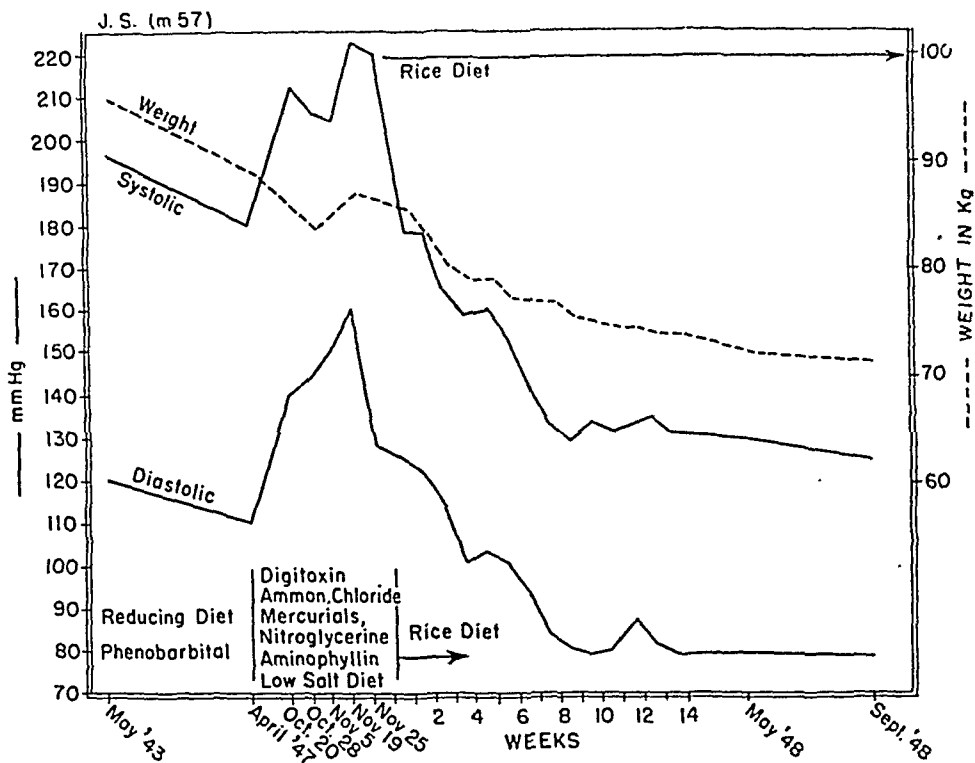


FIG. 19.

TABLE VIII

Changes of T<sub>1</sub> in 520 Patients with Hypertensive Vascular Disease after Rice Diet

Number of Patients	T <sub>1</sub> Before Rice Diet	T <sub>1</sub> After Rice Diet	Period on Rice Diet (Average)
No Change (388)			
68 34 286	Inverted Diphasic Upright	Inverted Diphasic Upright	7 months 8 months 11 months
Change in direction to inverted (10)			
0 5 5	Upright Diphasic Upright	Inverted Inverted Diphasic	8 months 4 months
Change in direction to upright (122)			
38 32 52	Diphasic Inverted Inverted	Upright Diphasic Upright	9 months 13 months 10 months

from 220/150 to 124/85 (figure 16) and the heart became normal in size within 10 weeks on the rice diet. Three years were required for the inverted  $T_1$  to become normally upright.

Figure 17 shows the reversal of an inverted  $T_1$  in the shortest period of time we have seen, one month. It is the electrocardiogram of a 23 year old man with hypertensive vascular disease, uncomplicated for three years, in the malignant phase with severe neuroretinopathy for three months. During the first month of the rice diet in which  $T_1$  became normal, the blood pressure

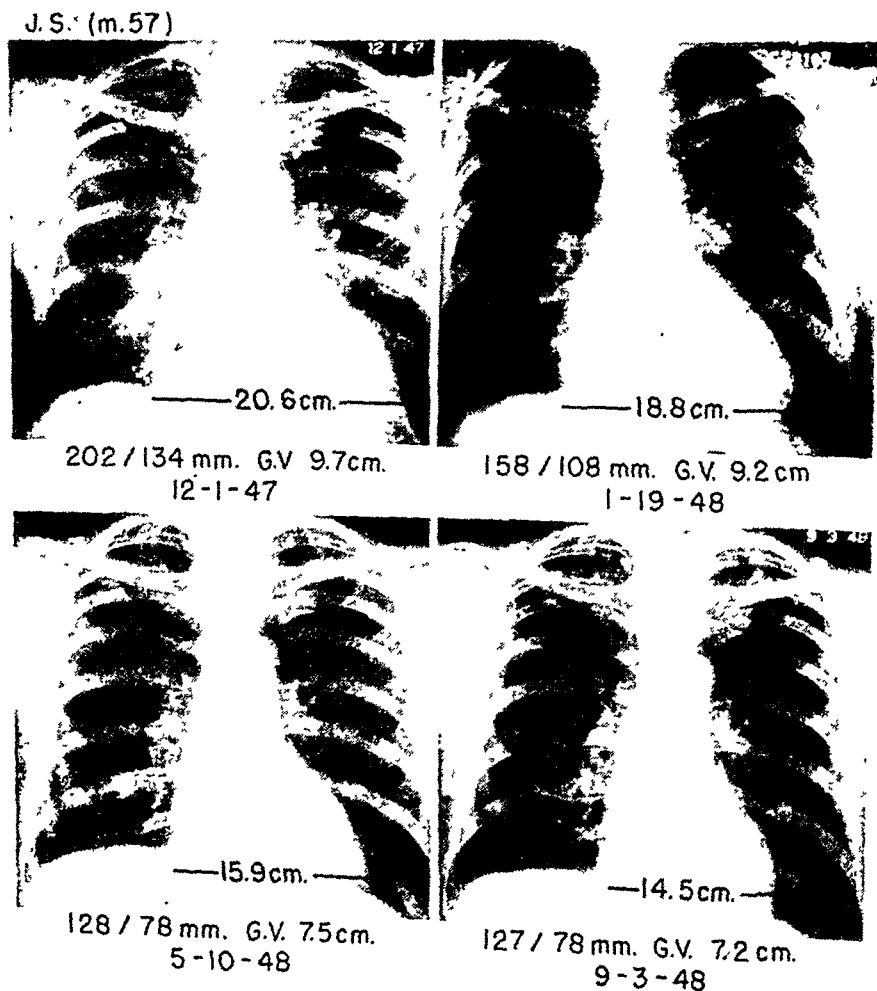


FIG. 20.

level decreased from an average of 222/148 to an average of 153/112. A normal blood pressure was reached only after two more months on the diet.

The T waves in Lead I were evaluated in 520 patients. None of these patients received digitalis or any other drug. All electrocardiograms were made with the patient at rest and in recumbent position. In 286 electrocardiograms which were normal at the start and in 102 electrocardiograms



which were abnormal at the start, no change occurred. In 132 electrocardiograms, a change did occur. In 10 in the direction from normal to-ward inverted. In 122 in the direction from abnormal to upright (table 8).

Figure 18 shows two chest films as an example of the reduction in heart size produced by the rice diet. It is the case of a 43 year old woman who had had hypertensive vascular disease for 14 years. It remained uncomplicated for 11 years. Then auricular fibrillation and heart failure developed with liver enlargement, edema, dyspnea and substernal pain. The

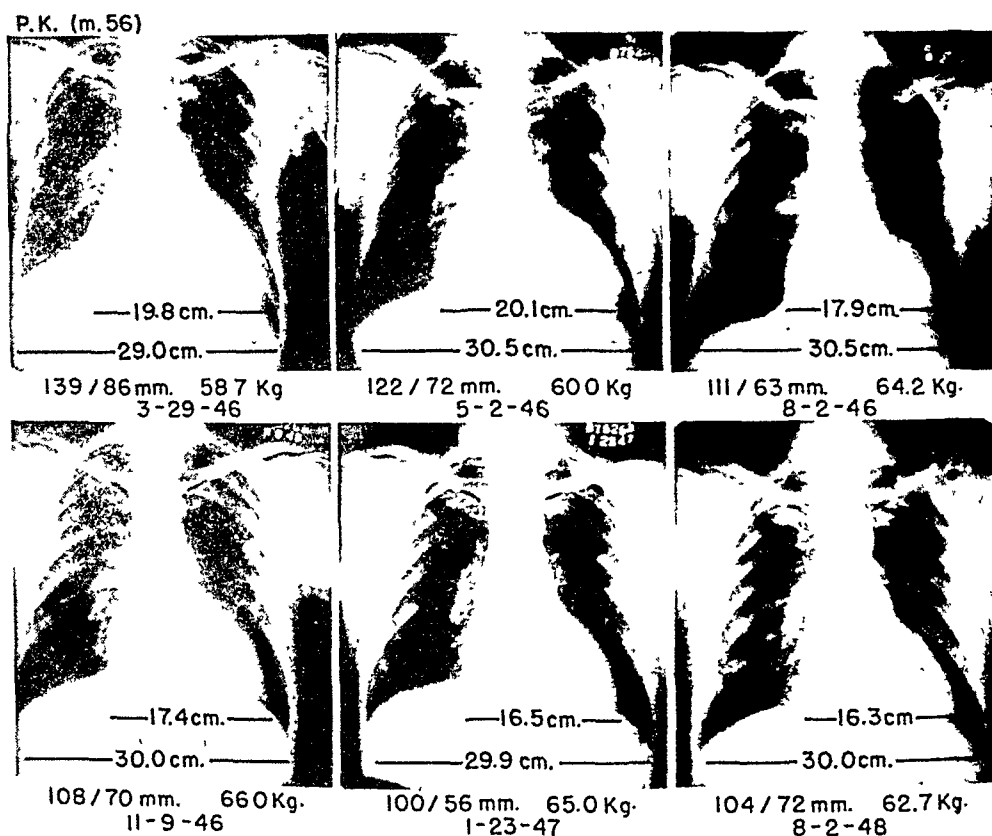


FIG. 21.

usual treatment with dietary restrictions, rest and digitalis was given with no improvement. Within eight months on the rice diet, the blood pressure decreased from 252/140 to 141/99, and the heart became smaller in size with a change in the transverse diameter of almost 40 per cent. The patient became asymptomatic and is now doing rather strenuous work.

The next case is an example of the length of time required for a heart which is enlarged and disfigured by the disease to change its size and shape back towards normal. The patient was a 57 year old man who had known he had hypertensive vascular disease for four years. Hypertensive heart

disease had become apparent in April, 1947. It was treated with digitoxin, ammonium chloride, mercurials, nitroglycerin, aminophyllin, weight reduction, salt-restricted diet. In spite of this medication and a weight loss of 30 pounds, the blood pressure increased and the heart failure became worse. When the patient came to us, the rice diet was started, and all medication including digitalis was immediately discontinued. The edema disappeared in 20 days; the blood pressure returned to normal in two months (figure 19). A decrease in heart size was noted after six weeks with a change in the transverse diameter of 8.7 per cent; after five months there was a change of 29 per cent; after nine months there was a change of 42 per cent (figure 20).

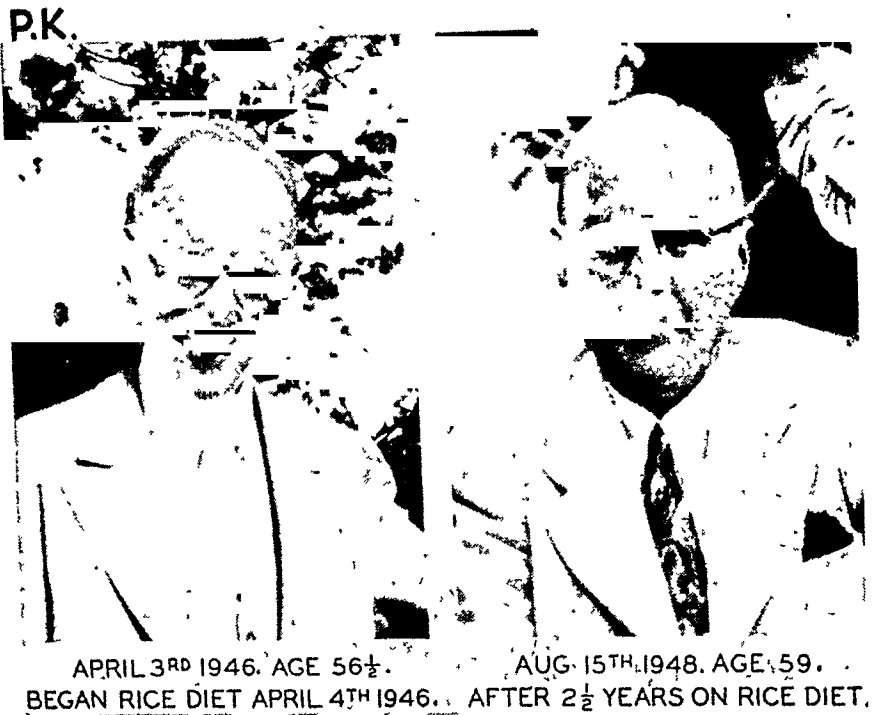


FIG. 22.

The patient became completely asymptomatic and has been without any medication for the past 14 months.

Chest films of 286 patients taken before and after one month or more of dietary treatment were measured for comparison (no digitalis or other drugs were given after the day the first chest film was taken). In 15 of the 286 patients (i.e. in 5 per cent), the heart became larger with an average increase of 2.6 per cent. In 146 patients there was a decrease in heart size with a change in the transverse diameter of 6.2 per cent (average), in 106 patients there was a decrease with an average change of 14.2 per cent and in 19 patients a decrease with an average change of 24.4 per cent (table 9).

I do not think that the improvement in the electrocardiographic pattern or the decrease in heart size or the disappearance of papilledema, hemor-

TABLE IX

Effect of Rice Diet on Heart Size: Average Changes in Transverse Diameter of Heart in 286 Patients with Hypertensive Vascular Disease

	Change		Average Period of Rice Diet (days)
	Diameter of Chest %	Transverse Diameter of Heart %	
15 patients with <i>increase</i> of 0-8.0%	+0.8	+ 2.6	184
146 patients with <i>decrease</i> of 0-9.9%	-0.7	- 6.2	112
106 patients with <i>decrease</i> of 10-19.9%	-0.3	-14.2	114
19 patients with <i>decrease</i> of 20% or more	-2.2	-24.4	187

Reprinted from the American Journal of Medicine, 4, April, 1948.

rhages, and exudates in the eyegrounds occurs as a simple consequence of a decrease in blood pressure. I have seen quite a few patients in whom these improvements have occurred in spite of the fact that the blood pressure remained at exactly the same level as before. They, likewise, occur in the many instances where vascular retinopathy and/or heart enlargement are present without hypertension.

Figure 21 is an example of the compensation of heart failure and the reduction of heart size in a patient who had gone through a fairly complete list of therapeutics. When he came to us in March, 1946, he was 56 years old. He had had nephrolithiasis and had developed hypertension and hypertensive heart disease. Nephrectomy on the left side was done in 1940 in

L.B. (m.56)

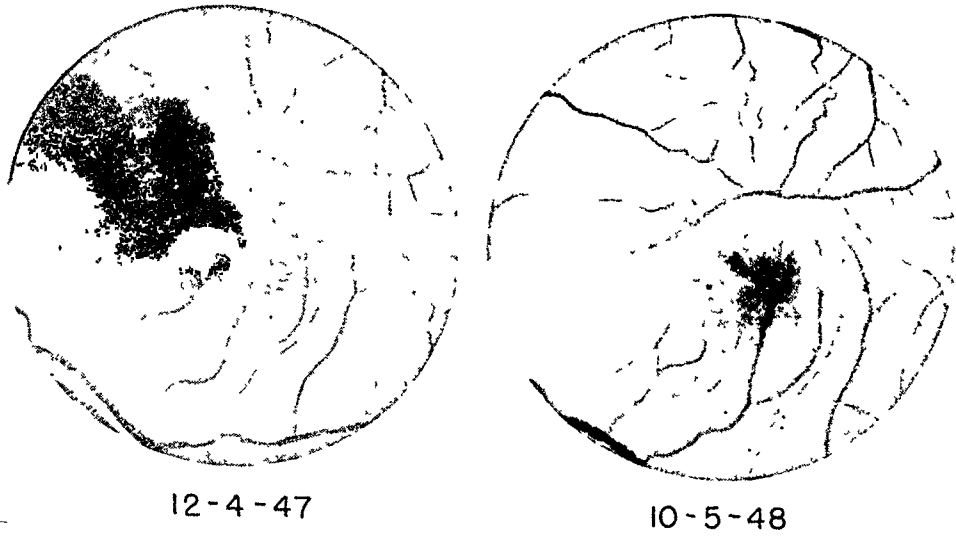
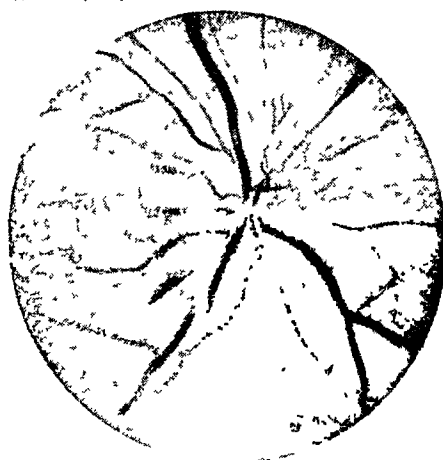


FIG. 23.

the hope of arresting his vascular disease. In spite of this, the disease continued and a left bundle branch block developed. When heart failure gradually increased, digitalis, squill, mercupurin, ammonium chloride, sedatives and salt-poor diet were tried.

The first chest film of March 1946, showed a greatly enlarged heart. There was edema, liver enlargement, and ascites. All medication was immediately discontinued and the rice diet started. Five weeks later the transverse diameter of the heart was 3 mm. larger, but the patient had lost most of his edema and was no longer dyspneic. The patient ate one pound of rice (dry weight) and one pound of dextrose daily and gained over 7 kg. during

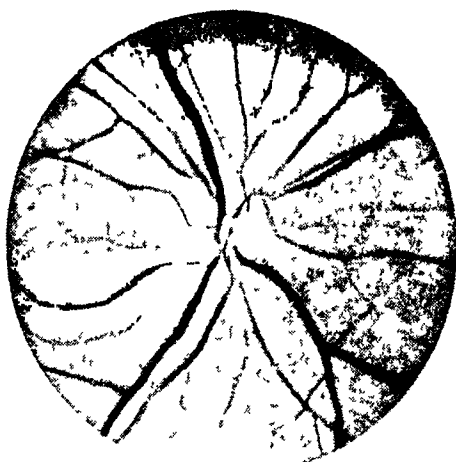
A.A.H (m, 47)



6-20-44

Blood pressure, average  
(June 20-July 20, 1944)

185/120



1-10-49

Blood pressure, average  
(January 10-11, 1949)

167/105

FIG 24.

seven months in spite of the loss of edema. Four months after the start of the diet the transverse diameter of the heart had decreased from 19.8 to 17.9 cm.; after seven months from 19.8 to 17.4 cm.; after 10 months from 19.8 to 16.5 cm. No medication has been given for the past three years. The patient is feeling well and is completely asymptomatic. The transverse diameter of the heart is now 16.3 cm., which means an overall change of more than 20 per cent. I showed the patient these heart pictures, boasting about the result. In return, the patient sent me a Christmas card with pictures of his face "before and after the rice diet" (figure 22). They are perhaps not uninteresting even from our mechanistic point of view. The first photograph shows the characteristic face of a patient with advanced heart disease,

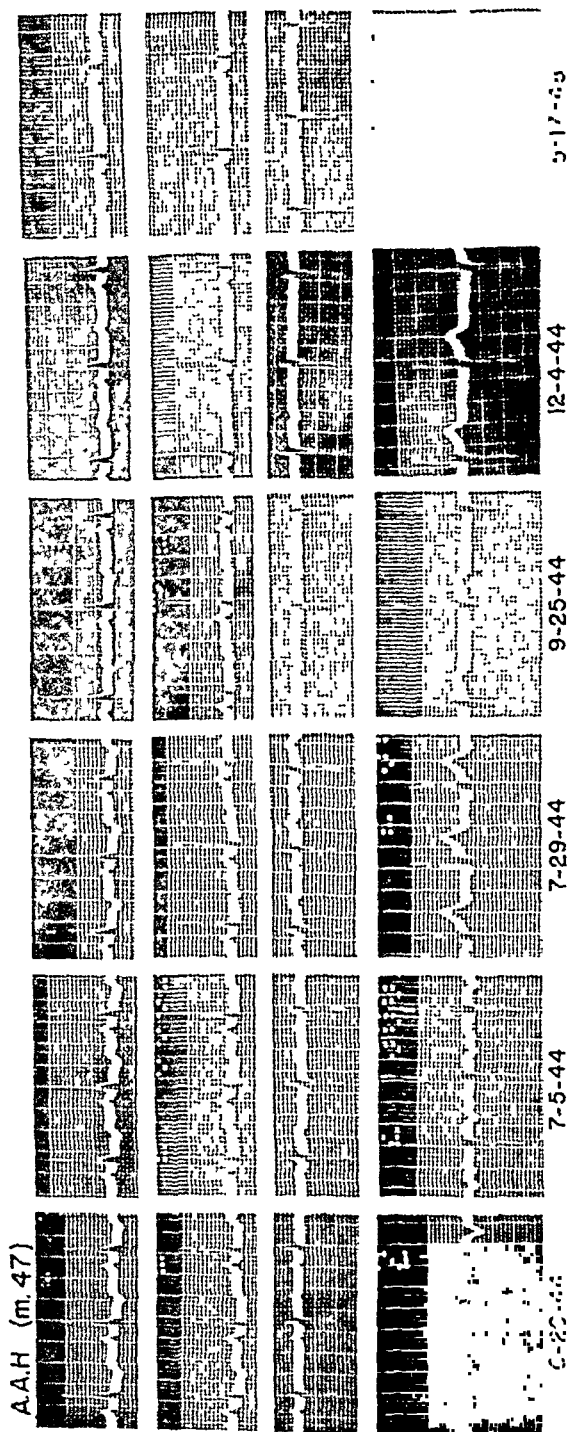
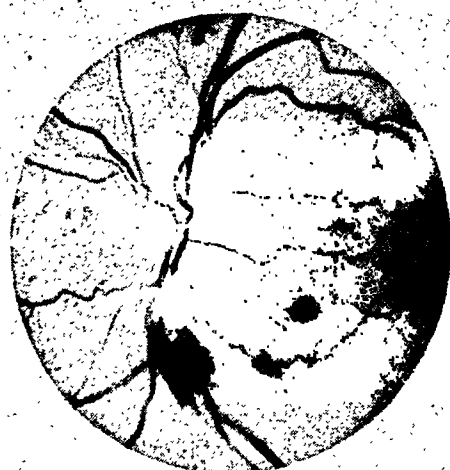
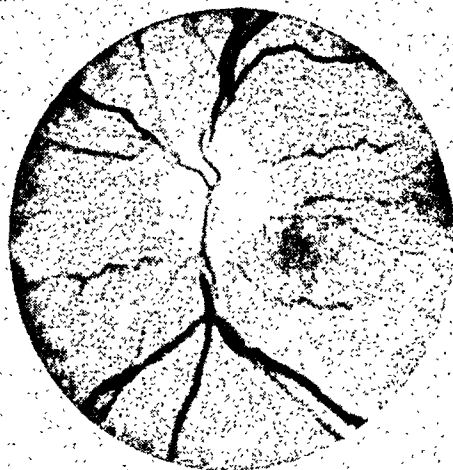


FIG. 25.

P.M. (m. 51)



217/153 mm. 10-31-47



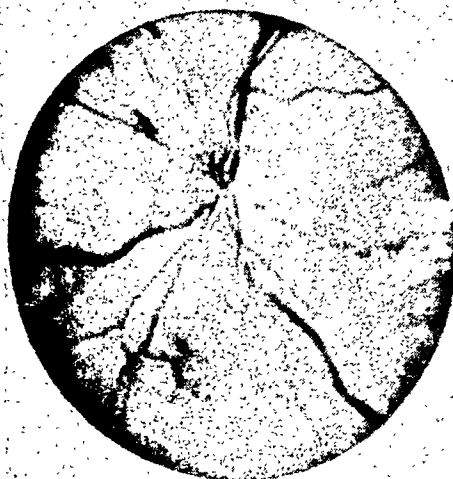
188/112 mm. 6-22-48

FIG. 26.

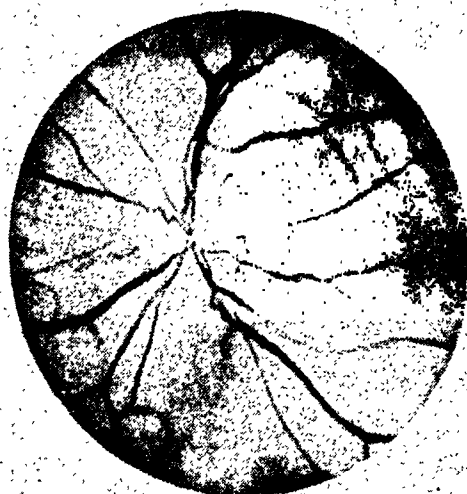
drawn, emaciated, prematurely aged, like that of a victim of starvation. The second photograph shows a well nourished, healthy man: one might say that the face has gained what the heart has lost.

Vascular retinopathy responds to the rice diet just as well as myocardial disease. The improvement of the retinopathy occurs no matter whether the blood pressure decreases or not.

L.W. (f. 45)



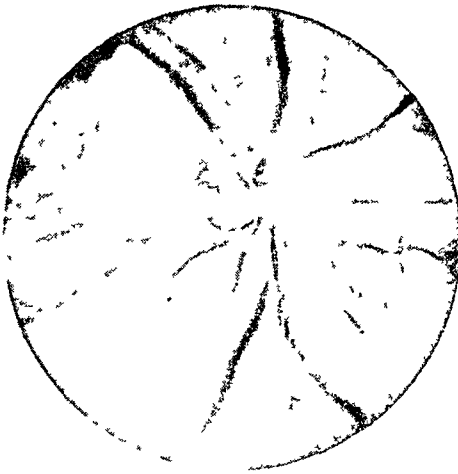
226/154 mm. 8-4-44



184/120 mm. 5-14-48

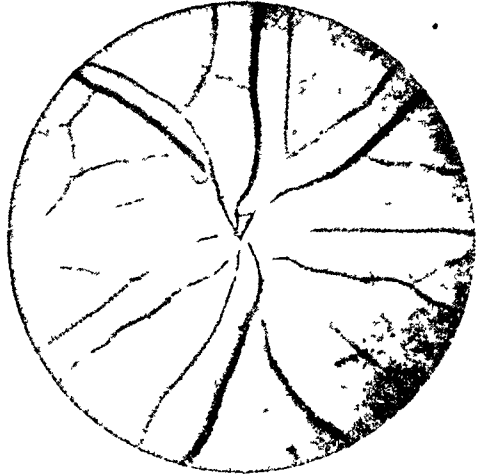
FIG. 27.

L.W. (f. 45)



226/154 mm.

8-4-44



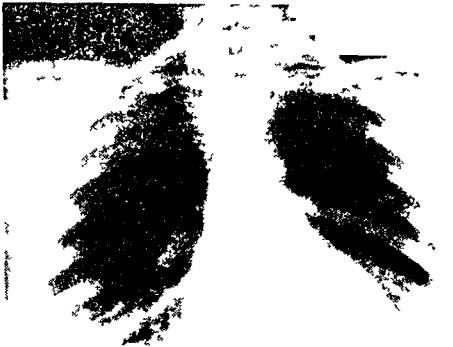
184/120 mm.

5-14-48

FIG. 28.

The eyeground pictures of three cases are shown as examples of the disappearance of papilledema, exudates, and hemorrhages, in spite of persistent hypertension. The first patient is a 56 year old man with hypertensive vascular disease which had been uncomplicated for 10 to 15 years. One month before he came to us he became blind in his left eye. The pictures (figure 23) show the disappearance of massive hemorrhages and exudates in 10 months on the rice diet. The patient regained his eyesight and is now well and active. The blood pressure has decreased but is still not normal.

L B (f. 24)



—16.6 cm.—

31.4 cm.

11-2-44



—12.9 cm.—

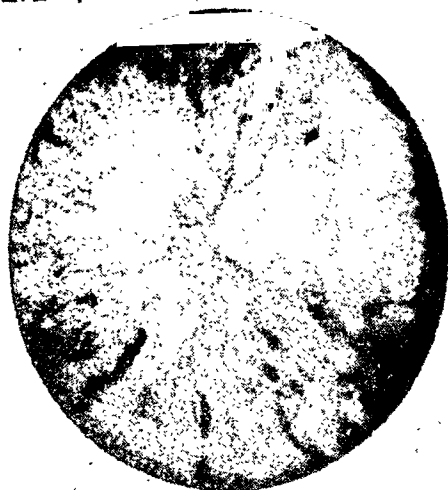
30.7 cm.

1-17-45

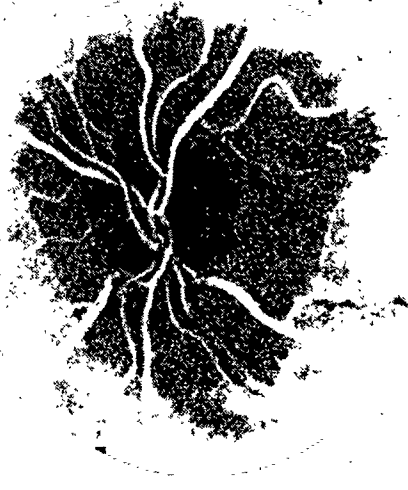
FIG. 29.

L.B. (f. 24)

LEFT



11-6-44



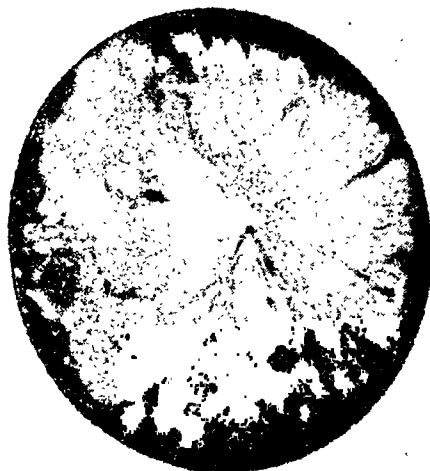
10-26-48

FIG. 30.

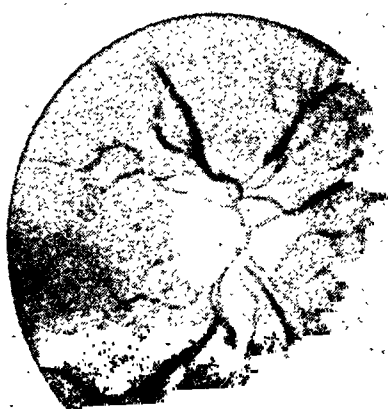
The second case is that of a man who was 47 years old when he came to us almost five years ago. He had been suffering from periodic attacks of severe headaches for years, but had known of his hypertension only for three months. He had not been conscious of any impairment of vision until I asked him to close his left eye and he found he was unable to read the headlines of a newspaper with his right eye. In one and one-half years of treatment with the rice diet, the exudates in the macula disappeared. The papilledema and hemorrhages cleared up completely and the eyesight was restored

L.B. (f. 24)

RIGHT



11-6-44



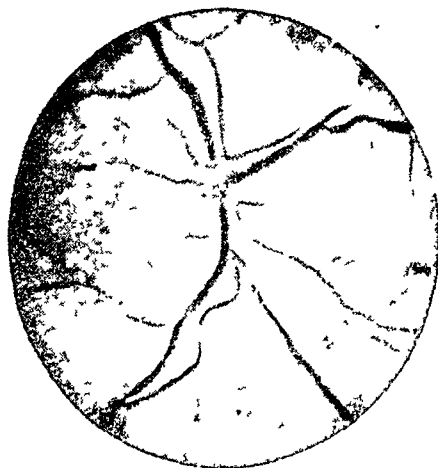
10-26-48

FIG. 31.

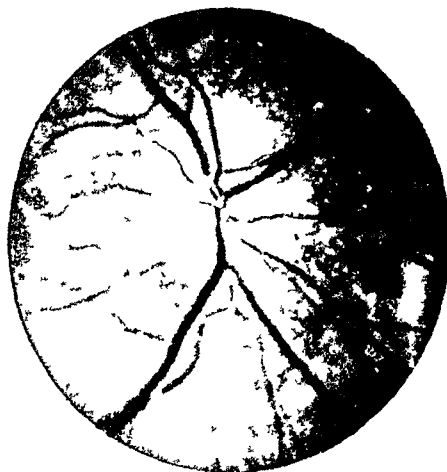


A. McA. (m.38)

RIGHT



2-11-46



2-14-49

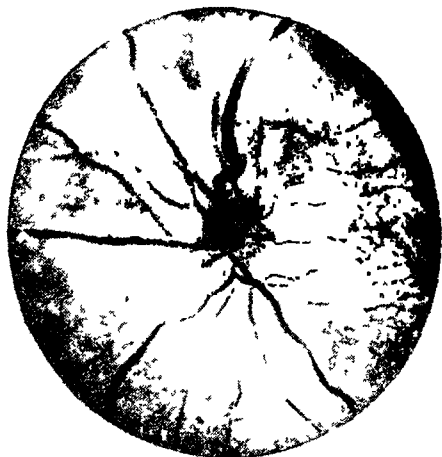
FIG. 32.

(figure 24). The heart, which was involved, also improved; the inverted  $T_1$  in his electrocardiogram became normally upright (figure 25). The blood pressure has decreased but is not normal.

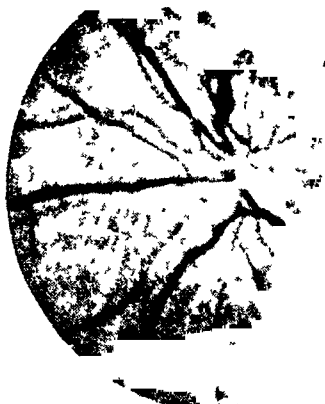
The third patient is a 51 year old man with hypertension known for 10 years. He had had progressive heart failure for seven months. There was hypertensive neuroretinopathy with papilledema, hemorrhages, and exudates, which cleared up in eight months on the rice diet (figure 26). The blood pressure did not become normal, but dropped from 217/153 to 188/112.

A. McA. (m.38)

LEFT



2-11-46



2-14-49

FIG. 33.

I have shown you pictures of patients who had essential hypertension with severe complications. We classify this type of hypertension as benign because of its slow course, although the term benign may lose its sense when the patient becomes blind from retinal disease or when he dies of heart failure, myocardial infarction, cerebral vascular accident or uremia. Moreover, the possibility always exists that any benign vascular disease may suddenly change into the malignant form. The last three patients whose eyeground photographs I showed you presented some of the signs said to be characteristic of malignant hypertension, the high diastolic blood pressure and

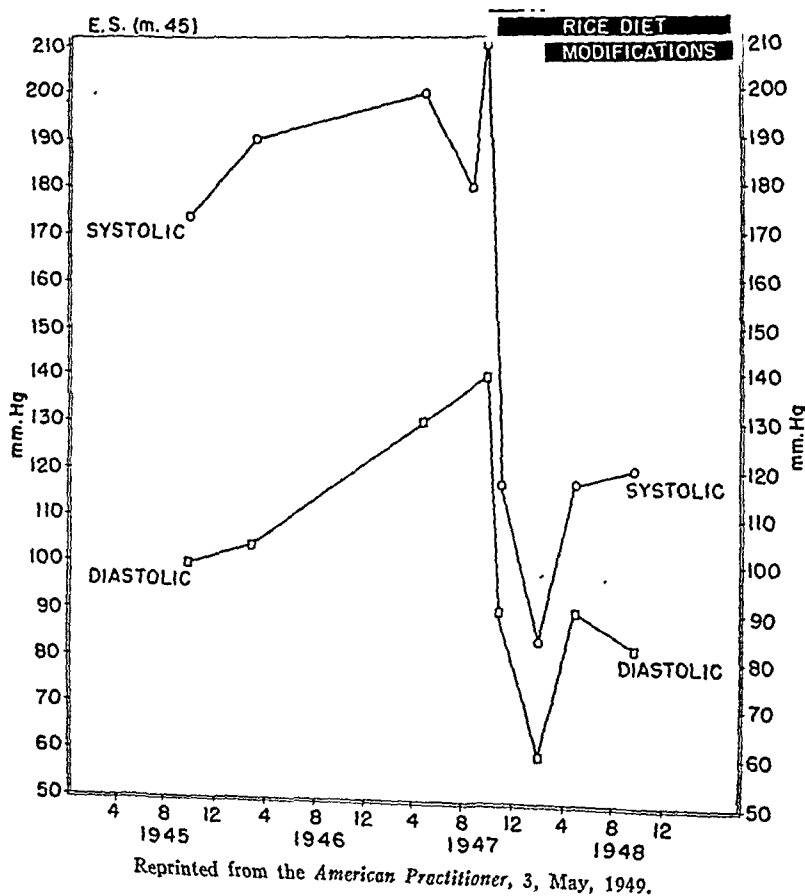


FIG. 34.

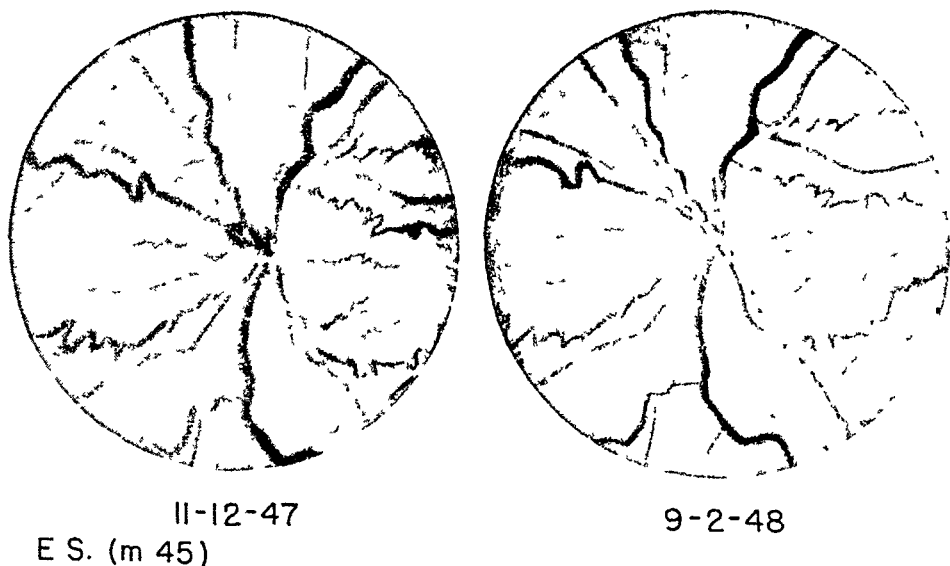
papilledema, hemorrhages and exudates. However, the eyegrounds did not show the picture of the explosive retinopathy which we associate with true malignant hypertension.

The following photographs are shown as examples of the effect of the rice diet on patients with full blown malignant hypertension.

The first case is that of a 45 year old woman who came to us in 1944 with a history of hypertension of four months' duration, apparently malignant from the onset. The eyegrounds show the typical picture of malignant neuroretinopathy. The patient followed the strict rice diet for one

year, then a modified rice diet. The blood pressure decreased from a level of 226/154 to a level of 184/120. The retinopathy healed completely (figures 27 and 28). Not only did the patient not die but after more than four and one-half years she is up and around and has no complaints.

The second patient is a 24 year old woman who had had an uncomplicated hypertension for five years. This benign hypertension had become malignant one month before she came to us (October, 1944). In 24 days on the rice diet, the blood pressure decreased from 233/157 to 118/80. The heart became smaller in size with a change in the transverse diameter of 22 per cent in 11 weeks (figure 29). Papilledema, hemorrhages and exudates disappeared in about three months. As the eyeground pictures of October, 1948, show, the retinopathy did not recur (figures 30 and 31). The



Reprinted from the *American Practitioner*, 3, May, 1949.

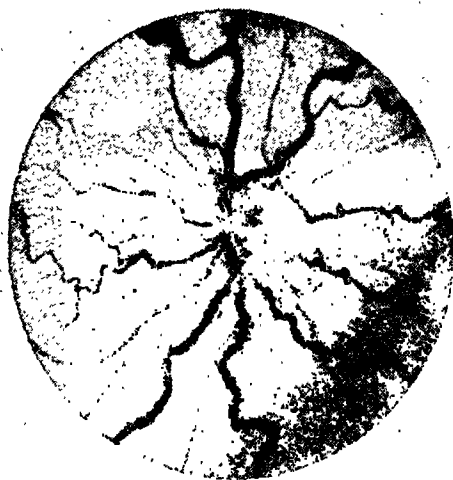
FIG. 35.

patient not only did not die of her malignant hypertension, but after more than four years is now well and doing strenuous work on her farm.

The third patient is a 38 year old man who had had hypertensive vascular disease for one year. The hypertension had been obviously malignant for about three months before he came to us. This case has been chosen as an example of a rather slow response to the rice diet. Definite improvement of the extensive neuroretinopathy was not seen until after one year. The inverted  $T_1$  in the electrocardiogram did not become upright until after two and one-half years, and it took almost three years for the blood pressure to come down to a significantly lower level (figures 32 and 33).

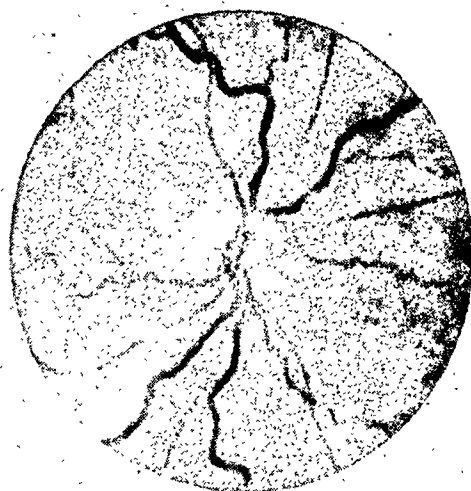
As a kind of summary, let me end with a case which shows not only the success but also the possible dangers of the rice diet. The patient, a busi-

ness man from New York, had had periodic check-ups since 1932 when he was 30 years old. The blood pressure had always been normal until 1941 when a slight elevation was noted. It climbed slowly during the following years. In 1945, it was 170/100, in 1946 190/100, in the Spring of 1947 190/130. In spite of this, the patient was completely asymptomatic. Both family physician and consultant specialist advised treatment with weight reduction, rest, sedatives and restriction of smoking. In September, 1947, the patient suddenly developed a severe headache with visual disturbances and consulted an ophthalmologist who found retinal hemorrhages, exudates, and papilledema and made a diagnosis of retinopathy of malignant hypertension. Another medical specialist was consulted who found a blood pressure of 202/144, confirmed the diagnosis of malignant hypertension and sent



11-12-47

E.S. (m. 45)



9-2-48

Reprinted from the *American Practitioner*, 3, May, 1949.

FIG. 36.

the patient to a surgeon in the New York Hospital for sympathectomy. The surgeon made the same diagnosis and recorded the same findings. After eight days of observation, a sympathectomy was scheduled for Monday, October 27, 1947. The evening before the operation, the patient decided to try the rice diet first and came to Durham. He presented the typical picture of malignant hypertension. The blood pressure was 210/140, in spite of sedatives; the eyegrounds showed extensive neuroretinopathy. On the rice diet, the blood pressure decreased rapidly. As a matter of fact, it decreased so much that after three months the patient had a blood pressure of 85/58 while lying and 60/30 while standing. A marked hypochloremia with elevation of urea nitrogen and non-protein nitrogen was found and the diet had to be modified greatly by the addition of toast, meat and all kinds of vege-

tables. The blood chemistry returned to normal and the blood pressure was regulated at a level of 110/77 within two weeks (figure 34). All the signs and symptoms of the malignant hypertension have disappeared; papilledema, retinal hemorrhages and exudates have cleared up completely; the engorged and tortuous veins are smaller in caliber and straighter (figures 35 and 36). However, not only the malignant but also the benign hypertension has disappeared. The blood pressure, which had been above normal for six years, is now (one and one-half years after the start of the rice diet) 116/76, although the patient has resumed playing his 18 holes of golf and eats a fairly liberal diet.

Ten years ago, I used to teach, what was generally taught and is still written in textbooks published as late as 1947, that the presence of advanced neuroretinopathy in malignant hypertension is an ominous prognostic sign indicative of the terminal stage of an irreparable disease. My experience with the rice diet has taught me that not only can so-called benign hypertensive vascular disease be effectively treated even when critical complications are present but also that malignant hypertension, in spite of advanced neuroretinopathy, may either be changed into the benign form of hypertension or made to disappear completely. The important result is not that the change in the course of the disease has been achieved by the rice diet but that the course of the disease can be changed.

# VIRAL HEPATITIS: PROBLEMS AND PROGRESS\*

By JOHN R. NEEFE, M.D., *Philadelphia, Pennsylvania*

THE problems associated with certain viral diseases of the liver have been the subject of intensive study during recent years. As methods permitting specific etiologic diagnosis are not available, the non-specific term "viral hepatitis" has been found useful for reference to the syndrome under consideration. "Viral hepatitis" thus includes those forms of hepatitis caused by hepatotropic, filterable, infectious agents which have not yet been identified with specific serological responses but which produce, as their outstanding manifestation, evidences of liver injury, which may or may not be associated with phenomena suggesting an infectious origin.

The available evidence indicates that at least two "virus-like" agents are concerned.<sup>1, 2</sup> One, hereafter referred to as virus IH, has been identified primarily with the clinical and epidemiological syndrome of infectious (epidemic) hepatitis. The other, hereafter referred to as virus SH, has been associated with the "homologous serum hepatitis" syndrome which characteristically develops two to five *months* after the occurrence of an opportunity for parenteral entry of the virus. The term "homologous serum hepatitis" really is an epidemiological term indicating the source of the infectious agent, but it unfortunately has acquired a misleading etiological implication in that the term has come to be synonymous with the hepatitis syndrome occurring after the long two to five month interval. However, virus IH also may be transmitted by blood or its products and be responsible for hepatitis after a two to six week interval. This syndrome also must be regarded as "homologous serum hepatitis," and it is therefore important to recognize that hepatitis syndromes occurring from two weeks to six months after exposure may be of viral origin and represent "homologous serum hepatitis."

The literature in recent years has been concerned almost entirely with the *advances* in knowledge concerning "viral hepatitis." It has seemed worthwhile, therefore, to refer briefly to some of the more important advances and then to devote the majority of the present discussion to a consideration of some of the remaining problems and current investigations directed toward their solution.

## RECENT ADVANCES

As the recent advances in knowledge concerning viral hepatitis have been reviewed in detail elsewhere,<sup>1, 2</sup> only those pertinent to the present discussion

\* Presented as a Morning Lecture at the Thirtieth Annual Session of The American College of Physicians, New York, N. Y., April 1, 1949.

From the Nutritional Service of the Gastro-Intestinal Section of the Medical Clinic and of the Department of Pediatrics, Medical School and Hospital of the University of Pennsylvania.

will be enumerated here. References to the original work and those responsible for it can be found in the review articles cited.

1. *Etiology*: (a) Differentiation of the two "virus-like" agents by means of studies in human volunteers; (b) Accumulation of information concerning certain of the physical properties of these agents including information indicating their resistance to many procedures which destroy or inactivate most bacteria and other viruses.

2. *Epidemiology*: (a) Demonstration of feces and blood as the principal human sources of the etiological agents; (b) Accumulation of evidence supporting the intestinal-oral route as a common mechanism of spread of the "IH type" virus; (c) Recognition of the rôle of blood and blood products as a source of both virus IH and virus SH and of various mechanisms of transfer of these viruses in blood to humans; (d) Demonstration that hepatitis virus may be water-borne and that certain methods of water disinfection may not be adequate under some circumstances; (e) Accumulation of data on incidence indicating the public health and military importance of the disease.

3. *Clinical Aspects*: (a) Establishment of the existence of a non-icteric form of the disease; (b) Elaboration of the clinical manifestations and their significance; (c) Recognition of the importance of hepatic tests and liver biopsy in diagnosis, management and prognosis; (d) Recognition that the disease may be associated with a significant mortality and morbidity and may be a cause of chronic liver disease; (e) Recognition of the possible association of certain etiologically obscure forms of chronic liver disease with previous apparent or inapparent infection with hepatitis virus.

4. *Prevention and Control*: (a) The discovery that human immune serum (gamma) globulin is highly effective in the prevention of virus IH hepatitis when administered to exposed persons during the incubation period prior to the onset of symptoms; (b) The recognition of certain mechanisms of transmission of hepatitis virus in blood, permitting the eradication of certain of those mechanisms; (c) Recognition of the potential danger of "water-borne" hepatitis virus and the unreliability of certain technics for disinfection of water; (d) Demonstration of the effectiveness of heat in the inactivation of hepatitis virus in human serum albumin solutions; (e) Development of a practical technic for large scale ultraviolet irradiation of plasma which has been effective in the inactivation of at least one strain of hepatitis virus in plasma.

#### CONSIDERATION OF CERTAIN REMAINING PROBLEMS

*Etiology*: To the present time, no extra-human host for hepatitis virus has been recognized. The human host, therefore, remains as only known source of hepatitis virus. Hepatitis virus IH would appear to account satisfactorily for most of the naturally occurring epidemics of hepatitis, certain cases of so-called "homologous serum hepatitis," and some sporadic cases. However, a large number of the sporadic cases occurring at the

present time are characterized by certain clinical features which are more consistent with the clinical syndrome that was observed in association with hepatitis virus SH under experimental conditions. As these differences in the clinical syndromes of virus IH and SH hepatitis, as observed experimentally, have been described in detail elsewhere,<sup>1, 3</sup> the summary in table 1

TABLE I

Clinical Differences between Virus IH and Virus SH Hepatitis as Observed in Volunteers

Observation	Virus IH	Hepatitis Virus SH
1. Type of onset	Abrupt	Insidious
2. Constitutional symptoms with onset	Marked	Minimal
3. Fever with onset	Present	Absent
4. Laboratory evidence of hepatic injury in association with clinical onset	Delayed 2 to 7 days	Often present before clinical symptoms

will suffice for the present discussion. Although it must be *strongly* emphasized that these differences are *not* sufficiently reliable or consistent to permit their use for clinical differentiation between virus IH and SH hepatitis, the similarity between the clinical features of many sporadic hepatitis cases and those of the virus SH syndrome leads one to suspect that some of them may be due to this virus. Thus, in a spot survey of approximately 250 cases of "viral hepatitis" hospitalized during June 1947 in the United States Army Hepatitis Center at Bayreuth, Germany (120th Station Hospital), Dr. W. Paul Havens, Jr. and I were impressed with the fact that approximately 85 per cent of the patients had had a relatively silent, insidious, almost asymptomatic, afebrile onset of jaundice. This contrasted strikingly with the usual type of onset of the naturally occurring disease observed in this and other overseas theatres during the recent war, namely a sharp, febrile onset associated with marked constitutional symptoms. In addition, it was found that almost all of the cases hospitalized in the Center at that time were sporadic, only a small proportion of the total cases having arisen in association with small, localized outbreaks. Perhaps of some significance was the fact that almost every patient in this group had had some exposure to the "syringe-needle" source of hepatitis virus during the six month period prior to the onset of the disease.

It seems reasonable, therefore, to suspect that at least some of the cases of sporadic viral hepatitis may be due to virus SH.

The possibility of an etiologic relationship between viral hepatitis and certain etiologically obscure forms of chronic liver disease, such as those illustrated by the following brief case abstracts, also is of considerable interest and importance.

*Case N92-49.* A 19 year old white female had a silent, asymptomatic, afebrile onset of jaundice with minor gastrointestinal symptoms during the spring of 1948.



Jaundice has persisted to the present time (one year) with only minor constitutional symptoms. Hepatic tests indicate moderately severe, active hepatic disturbance of the type associated with acute viral hepatitis. Needle liver biopsy reveals a dense infiltration of the portal triads with lymphocytes and plasma cells. Some of the lobules also show infiltration with these cells. A moderate increase in connective tissue is apparent in some of these triads with strands penetrating some of the lobules. The hepatic cells show varying stages of degeneration and regeneration.

*Case N96-49.* In 1945, an 18 year old male student reported that friends had noted scleral icterus. History and physical examination were negative except for scleral icterus and several recent transient episodes of upper abdominal discomfort, anorexia, and brief nausea. Hepatic tests revealed a retention type of jaundice. Tests for hemolysis were negative and the phenomena were thought to be most consistent with a diagnosis of so-called "physiological hyperbilirubinemia." From 1946 to the present time, he experienced one to two day periods of mild constitutional and gastrointestinal symptoms associated with hyperbilirubinemia (retention type); during the last year he occasionally has had a transient elevation of urine urobilinogen and intermittently positive "flocculation tests." These symptomatic episodes occurred once or twice each month. His interval health otherwise has been excellent. Liver biopsy revealed a normal architectural pattern. An apparent slight increase in the amount of fibrous tissue in a number of the portal triads was noted and several contained a definite infiltration with lymphocytes, histiocytes and plasma cells. In several areas, the connective tissue had the appearance of hyaline degeneration. A number of the hepatic cells had double nuclei and the appearance in certain areas suggested active regeneration of hepatic cells.

*Case N69-48.* This 47 year old white female developed pruritus, malaise, and minor gastrointestinal symptoms in the spring of 1947. The symptoms persisted and mild jaundice was noted several months later by a physician. In spite of a six month period of bed rest and all the therapeutic measures commonly employed in the management of chronic liver disease, the jaundice persisted and the serum albumin gradually decreased. When seen in the fall of 1948, she presented mild jaundice, numerous spider nevi, massive hepatomegaly (involving particularly the left lobe to an extent that suggested the presence of a focal lesion), and an enlarged spleen which filled the entire left abdomen from the costal margin to the pelvic inlet. Evidences of hypersplenism including moderately severe anemia, thrombocytopenia, and pronounced leukopenia were present. Hepatic tests revealed evidence of severe hepatic injury and liver biopsy revealed diffuse severe hepatic fibrosis, cellular infiltration, and various stages of degeneration and regeneration of hepatic cells.

It seems possible that these and certain other hepatic syndromes may represent clinical variants of chronic hepatitis initiated by the recognized, or other as yet unrecognized, strains of hepatitis virus. Determination of whether such chronic disease, if related to viral hepatitis, is the result of continued activity of the viral agent, or to some other process initiated by it, will be essential to the development of more effective methods of treatment.

Another clinical and etiological problem which may have some relationship to subclinical infection with hepatitis virus has become apparent during the course of studies on persons who have had varying degrees of recognized exposure to hepatitis virus. During the past two years, studies in our laboratory<sup>4</sup> in collaboration with Drs. Charles H. Kurtz, Hugo Dunlap Smith, John G. Reinhold and S. Clay Williams have revealed a surprisingly high incidence of laboratory findings suggesting mild hepatic disturbance in

groups of young adults who previously had had either maximal or minimal exposure to hepatitis virus without having developed clinically recognizable infections. The incidence of such findings in both groups has approximated 10 per cent. It is hoped that continued observation of these groups over a period of years will help to clarify the significance of the present subclinical abnormalities.

*Epidemiology:* Little additional information concerning the epidemiology of naturally occurring outbreaks of viral hepatitis has been obtained during the past two years. The probable importance of contaminated water as a source of some outbreaks deserves further emphasis. Epidemiological and experimental evidence of the natural transmission of hepatitis virus IH by this means was first reported in 1945 by the author and Dr. Joseph Stokes, Jr.<sup>5</sup> Subsequently, additional outbreaks have been traced to this source on the basis of epidemiological evidence and very recently Drs. John Farquhar and Joseph Stokes, Jr.<sup>6</sup> have studied a localized rural epidemic in which epidemiological data provided strong evidence that the virus was transmitted by water from a contaminated well.

In respect to the problem of *blood transmitted hepatitis virus*, evidence of the probable importance of the asymptomatic carrier is slowly accumulating. We have previously reported circumstantial evidence indicating that such a carrier was the source of a hepatitis virus that was present in a pool of mumps convalescent plasma in which his plasma had been included.<sup>7</sup> Experimental studies have shown conclusively that hepatitis virus was present, at least intermittently, in the blood of inoculated volunteers during the long asymptomatic interval between inoculation and the onset of clinically recognizable symptoms and signs of the disease.<sup>8, 9</sup>

Of particular interest in this respect is the recent recognition by Drs. J. Edward Berk and Leonard Malamut<sup>10</sup> of a professional donor who may represent a true asymptomatic long term carrier of hepatitis virus. Three of their patients who had developed the syndrome of homologous serum hepatitis had received blood from this professional donor at different times over an eleven month period during 1947-48. One of these patients had received no other blood or plasma. The onset in all three cases was approximately six weeks after transfusion. Subsequently, it was found that a patient who had received his blood in 1945 (no other blood or plasma) had developed jaundice within three months, the exact interval not being certain. Thus at least four cases of homologous serum hepatitis may be traceable to blood obtained from this professional donor at different times over a three year period. The donor had no history of recognized hepatitis or other liver disease. However, study of the donor by Berk and Malamut revealed the presence of hepatic dysfunction and a liver biopsy provided histologic evidence of chronic liver disease with diffuse fibrosis. The rôle of the hepatitis virus in the donor's hepatic disease is not clear as he also was a chronic alcoholic. It is hoped that transmission studies with this donor's serum, which are planned by Drs. Joseph Stokes, Jr. and John Farquhar in

collaboration with Drs. Berk and Malamut, will provide the needed confirmation of this important epidemiological observation. Of great interest and importance is the suggestive evidence of the existence of a carrier state over at least a three year period.

These observations provide further evidence of the probable frequency and importance of asymptomatic carriers in the epidemiology of this disease and the serious implications justify a reconsideration, at this time, of the general problems associated with blood transmitted hepatitis virus. Some of the factors contributing to the difficulties in solution of this problem are as follows <sup>1, 2</sup>:

1. Hepatitis virus may be present in high concentration in blood since minute quantities of plasma (.01 ml.) have induced the disease in volunteers.

2. Hepatitis virus may be present in blood without associated clinical symptoms or signs.

3. Whether viremia persists or recurs after recovery from acute hepatitis is not known.

4. No practical clinical method for demonstrating the presence of hepatitis virus in blood or its products has been developed.

5. Hepatitis viruses survive for long periods under widely varying conditions and resist many procedures which eliminate or inactivate many infectious agents.

6. Most procedures capable of inactivating or destroying hepatitis virus cannot be applied to blood or plasma without rendering them unsatisfactory for human use.

7. Active immunization against either virus IH or virus SH is not yet possible and human immune serum (gamma) globulin apparently does not afford passive protection against virus SH.

8. The disease has a high morbidity, may be responsible for the initiation of chronic hepatic disease, and has a significant mortality rate, particularly when superimposed on other conditions.

In view of these problems, a knowledge of the risk of transmission of hepatitis virus involved in the therapeutic use of blood and plasma becomes a matter of importance to all physicians. The lack of a specific diagnostic test, the difficulties of adequate follow-up have made the reliability of available data on the incidence of hepatitis following blood and plasma transfusion somewhat uncertain. However, the available information suggests that the minimal incidence of hepatitis associated with blood and plasma may be approximately as follows <sup>11, 12, 13</sup>:

Material	Incidence of Hepatitis
Whole Blood	0.6 to 0.8%
Small plasma pools (5-10 units)	1.5%
Large plasma pools (1000-5000 units)	4.5 to 12%

On the basis of these figures which do not include the cases of hepatitis without jaundice, there appears to be strong evidence of a serious risk in the use of large plasma pools and a smaller, but significant, risk in the use of either small plasma or whole blood pools. The risk of whole blood and small plasma pools often is increased by the frequent need for multiple transfusions by the same patient.

Unfortunately, the problems associated with hepatitis virus in blood extend beyond those involved in blood and plasma transfusion. The multiple opportunities for exposure to hepatitis virus of this origin are not generally recognized, the diagnosis frequently is not entertained in the absence of a history of transfusion, and some opportunities for prevention occasionally may be overlooked. It seems desirable, therefore, to cite some of the many potential sources of infection from blood:

1. *Purposeful parenteral introduction of blood or its products:*

- (a) Transfusions of blood, plasma, or serum.
- (b) Passive immunization with normal or convalescent blood, plasma, or serum.
- (c) Incorporation of plasma or serum into other biological products.
- (d) Therapeutic local application of blood or its products to open lesions.
- (e) Injection of certain products of human plasma fractionation.

2. *Accidental parenteral or oral introduction of blood or its products:*

- (a) Inadequately sterilized syringes, needles, lancets, and other instruments that come in contact with blood or its products and are used for:
  - 1. Intravenous, intramuscular, subcutaneous and intracutaneous injections (diagnostic, therapeutic and prophylactic procedures).
  - 2. Venous punctures for blood withdrawal only.
  - 3. Skin punctures (blood counts, other blood specimens, etc.)
- (b) Contamination of open skin and mucous membrane lesions or accidental ingestion of blood or its products through handling of blood specimens or blood-contaminated materials (excreta, wound discharges, etc.).

Contributing to the importance of the above sources is the fact that either IH or SH type virus may be present in blood and either the oral or parenteral route of entry therefore may be involved. Also pertinent to these considerations is the fact that in any infectious disease in which minute amounts of blood contain the agent, the possibility of mechanical or biological transmission by biting insects cannot be excluded. Although no definite evidence of transmission by biting insects has been obtained to date, a previously un-

reported observation is of some interest in relation to this question.<sup>14</sup> In 1945, an effort was made by the author and Dr. Joseph Stokes, Jr., in collaboration with Lt. William Jahnes, to obtain experimental evidence of mechanical or biological transmission of hepatitis virus by biting insects. A group of mosquitoes was allowed to feed alternately on a volunteer who was in the preicteric stage of experimentally induced virus IH hepatitis and a "normal" volunteer. The same mosquitoes subsequently were allowed to feed on three other volunteers after intervals of one, two, and four weeks. None of these volunteers developed definite evidence of hepatitis during the ensuing six months, although one of the group on which the mosquitoes fed after one to four weeks developed minor abnormalities with certain hepatic tests. These findings were not considered sufficiently distinctive to warrant a diagnosis of hepatitis. However, on subsequent oral challenge inoculation with known active virus IH, he proved to be resistant to infection. This tempts one to suggest the possibility that this man had been infected originally by the mosquitoes and had been immunized by subclinical infection. In retrospect, it is unfortunate that this mosquito experiment was conducted with our strain of virus IH as later studies showed that this virus was effective in inducing overt hepatitis with jaundice in only one of the nine volunteers injected by the parenteral route<sup>3</sup> although most of them apparently experienced a subclinical immunizing infection. Repetition of this experiment with virus SH, which was highly effective in inducing overt hepatitis when injected parenterally, would appear to deserve a high priority among future studies. The equivocal result of the study mentioned, if not coincidental, raises many interesting questions. Such a mechanism of transmission would provide a very tenable explanation for one of the epidemiologic mysteries associated with virus SH, namely, the mechanism for its natural perpetuation and survival prior to the development of man-made mechanisms for its dissemination.

Thus, it is possible that there are few persons who may not have had opportunities for exposure to blood borne hepatitis virus through one or another of these potential mechanisms.

While on this aspect of the subject, the increasing *medicolegal importance* of blood transmitted hepatitis virus warrants special comment. This matter has arisen because of the relationship between homologous serum hepatitis and certain indispensable technics of routine medical practice. In particular, the purposeful injection of blood and certain of its products involves a hepatitis risk which must be weighed against the existing indications for such injections. Attention to the preventable mechanisms of transmission which have been cited under the "accidental" mechanisms also is important in this respect. The unfortunate experience of an Italian physician recently described in a letter written by a foreign correspondent in Italy and published in the foreign correspondence section of the J.A.M.A.<sup>15</sup> illustrates this point:

"After a trial of more than one month and a verdict elaborated in sixteen hours, as reported in a previous letter, the physician of Varese who had been accused of disseminating by his imperfect technic an epidemic of 'syringe hepatitis' was sentenced to serve five years in prison, to discontinue practice for two additional years and to compensate the families of the victims, of whom 12 had died and an additional 100 were infected. The entire nation has been interested. The sentence seems terrible, for in 1946 nobody in Italy knew anything about infection with hematogenous hepatitis through imperfect sterilization of the syringe. The physician of Varese gave no less than 50 intravenous injections of a tonic to his patients every day.

"The trial had aroused the entire medical profession in Italy because the incriminated physician had an excellent reputation. The defense council will apply to the Court of Appeal, but for the moment the physician, who had enjoyed liberty conditionally, has been imprisoned."

Although it seems doubtful, on the basis of the evidence described, that the action taken in this case was justified, it serves to indicate the potential hazard involved.

As questions concerning the *control* of blood borne hepatitis virus frequently arise, it has seemed worthwhile to consider what preventive measures may be taken, on the basis of existing knowledge, in order to reduce the incidence of infections from this source.

I. *Detection of Infected Donors*: Such a preventive measure obviously would be of great value if it could be accomplished. Unfortunately, no practical method for rapid demonstration of hepatitis virus in blood has yet been developed. However, it appears that some infectious donors may present detectable evidence of clinical or subclinical hepatic injury. Such donors might be recognized by the routine performance of a relatively small group of laboratory tests. For this purpose, the following scheme is suggested:

1. Exclude donors with history of hepatitis or unexplained recent symptoms.
2. Physical examination with particular reference to liver.
3. Screening tests for hepatic disturbance:
  - a. *Before blood is drawn*:
    1. Urine bilirubin.
    2. Urine urobilinogen (sensitive simple methods are available).
    3. Exclude donor if either test positive.
  - b. *After blood is drawn but before blood is released*:
    1. Total and prompt direct reacting serum bilirubin.
    2. Cephalin cholesterol flocculation test (24 hr.).
    3. Thymol turbidity and flocculation tests.
    4. Do not release blood if any of these tests positive.

All professional donors periodically should have a careful "hepatic" history, a physical examination, and a bromsulfalein test in addition to the above group of tests.

Questions that are frequently asked are whether and when it is safe to use blood from a donor who has recovered from acute hepatitis. No evidence available to date permits an answer to these questions. It is not yet known whether viremia persists or recurs intermittently following acute hepatitis. Thus, the length of the various time intervals that have been adopted by certain blood banks as the minimum period that must elapse before acceptance of such donors is not based on factual evidence and merely represents an attempt to take a reasonable precaution. It would seem more logical, in the absence of definite knowledge concerning this point, to exclude as donors all persons known to have had this disease.

II. *Inactivation of Hepatitis Virus in Blood and Blood Products:* Until some method for detecting hepatitis virus in blood and its products becomes available, it will not be possible to solve this problem by exclusion of infected units. Even with the employment of the methods of donor selection suggested above, carriers who have no history of apparent infection and present no laboratory indications of hepatic disturbance must be presumed to exist and will escape detection. Therefore, the main hope in this field of prevention lies in the development of some method for inactivation of hepatitis virus in blood and its products. The resistance of hepatitis viruses to methods or conditions which inactivate or eliminate many pathogens makes this a formidable problem as most procedures that are capable of inactivating hepatitis virus also are injurious to blood and plasma. In an effort to find some solution to this problem, Oliphant first suggested in 1944 the possible usefulness of ultraviolet irradiation of plasma for inactivation of hepatitis virus in plasma.<sup>16</sup> Since that time, substantial improvements have been made in the technics for irradiation of plasma. Studies by Hampil and Spizizen, in the Sharp and Dohme Laboratories, demonstrated the effectiveness of this procedure in inactivating certain other viruses in plasma.<sup>17</sup> In collaboration with these workers, Blanchard, Stokes, and Wade recently have provided evidence that this method was effective in inactivating one strain of virus SH in plasma.<sup>17</sup> It would appear, therefore, that carefully controlled ultraviolet irradiation of plasma may provide one means of decreasing the incidence of this disease. It should be pointed out, however, that only one strain of hepatitis virus has been tested to date and that this was not a highly potent strain. Additional confirmatory studies thus are urgently needed before ultraviolet irradiated plasma can be accepted as free from the risk of viable hepatitis virus. Even if subsequent studies establish its effectiveness, ultraviolet irradiation is not a convenient or desirable solution to this problem, as the technical difficulties involved are substantial, its use must be restricted to centers where special equipment and technical experts are available, and the present technic is not applicable to whole blood. A more generally useful method is needed and the most

promising hopes for this originate from recent observations which suggest that some viruses may be destroyed by small quantities of certain chemical agents which can be added to blood or plasma without serious alterations of these substances or danger to the human recipient of materials so treated.<sup>18</sup>

III. *Prevention of the Disease in Recipients of Blood and Its Products:* The ability of human immune serum (gamma) globulin to prevent virus IH hepatitis when injected in the incubation period prior to the onset of the disease was demonstrated in 1944 by Dr. Joseph Stokes, Jr. and the author.<sup>1, 19</sup> Its effectiveness has since been confirmed by other investigators in four additional epidemics occurring in widely separated areas both in this country and abroad,<sup>1, 2</sup> the most recent confirmation being provided by Drs. John Farquhar and Joseph Stokes, Jr. in an institutional epidemic occurring in 1948.<sup>6</sup> These investigators also obtained some evidence through this same study which suggested that persons who received gamma globulin during the incubation period, or were exposed shortly after receiving gamma globulin, experienced an inapparent infection which resulted in active immunization.<sup>20</sup> That such immunization can occur from subclinical infection has been demonstrated experimentally in studies previously reported by the author in connection with Dr. Sidney S. Gellis and Dr. Joseph Stokes, Jr.<sup>3</sup> In this study, volunteers who failed to develop clinically detectable signs of active infection after parenteral inoculation with virus IH were subsequently found to be resistant to oral challenge inoculation with highly active virus IH. The possibility of accomplishing active immunization by a proper combination of gamma globulin and attenuated hepatitis virus has been suggested by Dr. Stokes and this deserves prompt exploration and study.<sup>20</sup>

Unfortunately, the usefulness of human immune serum globulin in the prevention of virus IH infections apparently does not extend to virus SH infections,<sup>21</sup> which appear to be the most frequent problem associated with blood or plasma transmission. Although the studies to date indicate that even large and repeated doses of gamma globulin fail to prevent virus SH hepatitis, the fact that some blood transmitted infections are due to virus IH probably warrants the use of prophylactic injections of gamma globulin in association with multiple transfusions of blood and non-irradiated plasma. This also appears desirable as a prophylactic measure in recognized exposures occurring through the "accidental" mechanisms. In this respect, it seems desirable to emphasize the fact that careful follow-up studies of several thousand persons injected with gamma globulin have failed to reveal any evidence that this material itself has been a source of either virus IH or SH infections.<sup>21</sup>

IV. *Reduction of Incidence by Selection of Materials:* It is evident from the foregoing that none of the methods of prevention thus far described can be depended upon to eliminate the hazard of viral hepatitis at present inherent in the use of blood and certain of its products. Gamma globulin



and the currently used heat treated human serum albumin solutions apparently can be regarded as free from this risk.<sup>22</sup> The data described above indicate that the risk of hepatitis is greater with some blood products than with others and suggest that a reduction in incidence may be accomplished by limiting, as much as possible, the use of those associated with greater risk.

When indications and availability permit, the choice of materials for transfusion might be based on the following tentative plan:

1. *Minimal risk:*

- a. Human serum albumin solution (heat treated).
- b. Ultraviolet irradiated plasma???

2. *Small risk:*

- a. Whole blood and single plasma units.

3. *Moderate risk:*

- a. Small plasma pools.
- b. Multiple transfusions of whole blood or single plasma units.

4. *Maximal risk:*

- a. Large plasma pools.

The exact place of irradiated plasma in this list is uncertain. As this method usually is applied only to relatively large plasma pools and its consistent effectiveness has not been demonstrated, it does not seem wise to promote its widespread use until additional information becomes available. Recent studies by Janeway and his associates indicating that the anti-hemophilic fraction of blood plasma has been a source of hepatitis virus have been cited elsewhere.<sup>21</sup>

V. *Prevention of "Accidental Mechanisms" of Transmission:* The prevention of certain of the "accidental mechanisms" described above obviously is possible but involves difficult and costly changes in certain everyday medical technics. Reliable information concerning the frequency of transmission by these mechanisms is not available. However, sound epidemiological evidence of transmission by improperly sterilized syringes and needles exists<sup>23, 24</sup> and the hazard therefore must be recognized. Until it becomes possible to prove that the frequency is so small as to be negligible, it would seem that no choice exists concerning recommendations in this matter and that individual properly sterilized syringes, needles, and other instruments that penetrate the skin should be used for each patient.

As information concerning the effect on the hepatitis viruses of various methods of sterilization is lacking, it is difficult to define "adequate" sterilization in respect to this problem. The available experimental evidence bearing on this point is as follows<sup>1</sup>:

1. Hepatitis virus in serum albumin solution was inactivated by heating at 60° C. for 10 hours.
2. Hepatitis virus in contaminated water was inactivated by "break-point" chlorination.

Neither of these studies provided information concerning the minimal requirements for inactivation of the virus by either method but they do indicate the susceptibility of hepatitis virus to inactivation by proper exposure to heat and chemicals. Obviously the presence of blood clots and other foreign materials tends to interfere with exposure of the hepatitis virus to disinfecting agents. Thus, proper and thorough cleansing of syringes, needles, and other instruments is of primary importance. If this is well done, it is probable that complete immersion in boiling water for five minutes would represent "adequate" sterilization. Likewise, if care is taken to insure complete contact of all surfaces of thoroughly cleansed syringes, needles, lancets, etc. with potent chemical disinfectants for at least one hour, it seems reasonable to assume that "adequate" sterilization would result. In my opinion, however, heat sterilization should be employed whenever possible and the autoclave would be the method of choice.

Prevention of infection from contact with blood or blood contaminated materials or objects involves precautions of such magnitude that special measures other than reasonable care appear justifiable only in respect to patients with recognized or suspected hepatitis.

### SUMMARY AND CONCLUSION

"Viral hepatitis" is presented as a syndrome caused by at least two, primarily hepatotropic, filterable, infectious agents (Viruses IH and SH) which have not yet been associated with specific serological responses but which produce, as their outstanding manifestation, evidences of liver injury, with or without phenomena suggestion an infectious origin. Some of the major advances in knowledge concerning etiology, epidemiology, clinical aspects, and prevention are enumerated and certain of the remaining problems are discussed. The possible relationship of hepatitis viruses to certain etiologically obscure types of hepatic disease and the possible rôle of virus SH in the etiology of so-called sporadic hepatitis are considered. The problems associated with blood transmission of hepatitis viruses are reviewed and possible methods of reducing the incidence of infections from this source are considered. The data presented herein clearly indicate that many important aspects of the problem of viral hepatitis remain to be solved.

### BIBLIOGRAPHY

1. NEEFE, J. R.: Recent advances in the knowledge of virus hepatitis, *Med. Clin. N. Am.*, 1946, 1407-1443, Philadelphia number.
2. HAVENS, W. P., JR.: Infectious hepatitis, *Medicine*, 1948, xxvii, 279-326.

3. NEEFE, J. R., GELLIS, S. S., and STOKES, J., JR.: Homologous serum hepatitis and infectious (epidemic) hepatitis: Studies in volunteers bearing on immunological and other characteristics of the etiological agents, *Am. Jr. Med.*, 1946, i, 3-22.
4. NEEFE, J. R., KURTZ, C. H., SMITH, H. D., REINHOLD, J. G., and WILLIAMS, S. C.: To be published.
5. NEEFE, J. R., and STOKES, J., JR.: An epidemic of infectious hepatitis apparently due to a water borne agent, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 1063-1075.
6. FARQUHAR, J., and STOKES, J., JR.: Personal communication.
7. NEEFE, J. R., STOKES, J., JR., and GELLIS, S. S.: Homologous serum hepatitis and infectious (epidemic) hepatitis: experimental study of immunity and cross immunity in volunteers, *Am. Jr. Med. Sci.*, 1945, ccx, 561-575.
8. NEEFE, J. R., STOKES, J., JR., REINHOLD, J. G., and LUKENS, F. D. W.: Hepatitis due to the injection of homologous blood products in human volunteers, *Jr. Clin. Invest.*, 1944, xxiii, 836-855.
9. PAUL, J. R., HAVENS, W. P., JR., SABIN, A. B., and PHILIP, C. B.: Transmission experiments in serum jaundice and infectious hepatitis, *Jr. Am. Med. Assoc.*, 1945, cxxviii, 911.
10. BERK, J. E., and MALAMUT, L.: Personal communication.
11. SPURLING, N., SHONE, J., and VAUGHAN, JR.: Incidence, incubation period, and symptomatology of homologous serum jaundice and infectious hepatitis, *Brit. Med. Jr.*, 1946, ii, 409-412.
12. BRIGHTMAN, I. J., and KORN, R. F.: Homologous serum jaundice in recipients of pooled plasma, *Jr. Am. Med. Assoc.*, 1947, cxxxv, 268-272.
13. MACCALLUM, F. O.: Proceedings of the fourth international congress on tropical medicine and malaria, May 10-18, 1948, Washington, D. C., in press.
14. NEEFE, J. R., STOKES, J., JR., and JAHNES, W.: Unpublished data.
15. Foreign correspondence, *Jr. Am. Med. Assoc.*, 1948, cxxxvii, 1077.
16. OLIPHANT, J. W.: Jaundice following administration of human serum, *The Harvey Lecture Series*, 1943-44, xxxix, 254.
17. STOKES, J., JR., BLANCHARD, M., HAMPIL, B., SPIZIZEN, J., and WADE, G. R.: Methods of protection against homologous serum hepatitis. II. The inactivation of hepatitis virus SH with ultraviolet rays, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 341-343.
18. HARTMAN, F. W., MANGUM, G. H., FEELEY, N., and JACKSON, E.: On the chemical sterilization of blood and blood plasma, *Proc. Soc. Exper. Biol. and Med.*, 1949, lxx, 248-254.
19. STOKES, J., JR., and NEEFE, J. R.: The prevention and attenuation of infectious hepatitis by gamma globulin, *Jr. Am. Med. Assoc.*, 1945, cxxvii, 144-145.
20. STOKES, J., JR.: Rachford Lectures, *Viral Hepatitis, Part I and Viral Hepatitis, Part II*, February 1-2, 1949, Cincinnati.
21. BLANCHARD, M., STOKES, J., JR., NEEFE, J. R., GELLIS, S. S., and WADE, G. R.: Methods of protection against homologous serum hepatitis, Part I, Studies on the protective value of gamma globulin in homologous serum hepatitis SH virus, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 336-341.
22. GELLIS, S. S., NEEFE, J. R., STOKES, J., JR., STRONG, L. E., JANEWAY, C. A., and SCATCHARD, G.: Chemical, clinical, and immunological studies on the products of human plasma fractionation. XXXVI. Inactivation of the virus of homologous serum hepatitis in solutions of normal human serum albumin by means of heat, *Jr. Clin. Invest.*, 1948, xxvii, 239-244.
23. Editorial: Syringe-transmitted hepatitis, *Jr. Am. Med. Assoc.*, 1949, cxxxix, 459.
24. NEEFE, J. R.: Viral hepatitis, a consideration of certain aspects of current importance to the practicing physician, *New Eng. Jr. Med.*, 1949, ccxi, 445-448.

# THE CLINICAL MANIFESTATIONS AND LABORATORY DIAGNOSIS OF RICKETTSIALPOX \*

By HARRY M. ROSE, M.D., *New York, N. Y.*

RICKETTSIALPOX, the newest member of the human rickettsioses, was first observed in 1946<sup>1,2</sup> and thus far has been confined exclusively to the metropolitan area of New York City. The etiological agent was identified by Huebner and his associates<sup>3</sup> as *Rickettsia akari*, a new species which is serologically related to the spotted fever group of rickettsiae. The disease is apparently transmitted to man by a blood-sucking mite, *Allodermanyssus sanguineus*, an arthropod parasite of rodents.<sup>4</sup> *Rickettsia akari* has been isolated from pools of these mites collected in dwellings where cases of rickettsialpox have recently occurred. The tropical rat mite, *Liponyssus bacoti*, has also been shown experimentally to be a potential vector,<sup>5</sup> although its rôle in the natural transmission of the disease is undetermined at the moment. An animal reservoir of the infection exists in the common house mouse, *Mus musculus*,<sup>6</sup> and the associated occurrence of rickettsialpox with the rodent infestation of dwellings has been well established.<sup>7</sup>

Rickettsialpox continues to be seen frequently in New York City, especially in upper Manhattan and the Bronx, although only a few cases have occurred in Brooklyn and none have been recognized on Staten Island. In the past three years nearly 500 cases have been reported to the Bureau of Preventable Diseases, New York City Department of Health,<sup>8</sup> and many others have undoubtedly escaped recognition, especially those of mild or atypical character. Since the spring of 1947, 35 proved cases of rickettsialpox have been seen at the Columbia-Presbyterian Medical Center of which 22 were admitted to the hospital and 13 were followed in the out-patient department. These cases furnish the basis for the present communication, which deals with the clinical manifestations of the disease and the methods employed in the laboratory for specific serologic diagnosis and for the isolation of the responsible agent. Brief reference is also made to the results of treatment with aureomycin in two patients and with streptomycin in one patient.

## CLINICAL MANIFESTATIONS

The general clinical features of rickettsialpox have been previously described.<sup>9</sup> The onset of the illness is usually characterized by the appearance of a primary cutaneous lesion at the site of inoculation by the arthropod vector. About a week later the patient develops fever, chills, malaise and

\* Presented at the Thirtieth Annual Session, American College of Physicians, New York, N. Y., March 30, 1949.

From the Departments of Medicine and Bacteriology, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.

headache, followed shortly by a secondary papulovesicular cutaneous eruption which may resemble the rash of varicella. Although the constitutional symptoms may be severe and prolonged for a week or more, the disease is benign and no deaths have occurred.

The common course of the disease may be illustrated by the following brief case report:

The patient was a 50 year old white female who entered the hospital on May 6, 1948, complaining of fever, headache, malaise and a cutaneous eruption of one week's duration. Two weeks before admission she first noticed a small papular lesion on the inner aspect of the right upper arm. This lesion became progressively larger during the next few days. About a week later she began to experience alternate sensations of chilliness and heat, and found her oral temperature to be 102°. At the same time she developed an increasingly severe frontal headache, a slight non-productive cough and malaise. Five days before admission she noted the appearance of a generalized skin eruption. In the interim the temperature continued to fluctuate between 102° and 104°, the headache persisted and she experienced several shaking chills. On entrance to the hospital she did not appear acutely ill. The temperature was 101.6°, pulse 80, respirations 18 and arterial pressure 130 mm. Hg systolic and 80 diastolic. A rash was present over the face, trunk and extremities consisting of widely spaced erythematous papules from 2 to 4 millimeters in diameter, most of which showed small vesicles at their summits. On the inner surface of the right arm, just above the elbow, there was an erythematous lesion about 1.0 centimeter in diameter with a central blackish crust. The eruption was neither painful nor pruritic. The conjunctivae were clear. There were no petechiae. One vesicular lesion was seen on the soft palate just to the left of the midline. A few enlarged, slightly tender lymph nodes were palpated in the right axilla, but otherwise there was no lymphadenopathy. The lungs were clear. The heart was not remarkable. The abdomen was negative and the spleen was not enlarged.

The laboratory findings were as follows: Hemoglobin 15.0 grams, erythrocyte count 4,300,000, leukocyte count 4,240 with polymorphonuclears 58 per cent, lymphocytes 38 per cent, monocytes 2 per cent and eosinophiles 2 per cent. No abnormal leukocytes were seen in the smear. The urinalysis, Kline test and chest roentgen-ray were negative. The erythrocyte sedimentation rate (Westergren method) was 26 millimeters in one hour.

The patient's course in the hospital was uneventful. The temperature fell to normal in 36 hours, the rash rapidly faded and she was discharged on the morning of the fourth day.

The rickettsialpox complement fixation test on a sample of blood collected on the day of admission was negative. The test was positive in a serum dilution of 1-32 on a specimen of blood taken three weeks later.

*Incubation Period.* The incubation period of rickettsialpox has not been well established. One patient developed fever nine days after an apparently single exposure to a known focus of an infection.<sup>1</sup> In another individual who acquired the infection accidentally in the laboratory, the exact time of a single exposure was known.<sup>10</sup> This person developed a primary lesion on the seventh day, fever on the tenth day and a secondary eruption on the twelfth day after exposure. The interval between the time of infection and the appearance of the systemic reaction thus may be 9 or 10 days, although both shorter and longer periods of incubation probably occur.

*Age and Sex Incidence.* As in most infectious diseases which are unrelated to occupation, rickettsialpox has no predilection for either sex. In the present series of 35 cases, 18 were females and 17 were males. The ages of the patients ranged from two to 56 years.

Eighteen of the 35 cases occurred in persons of the negro race, a much larger proportion than would be expected among general admissions to this hospital. The high incidence among colored patients is probably a reflection of their economic status and the fact that their living quarters are usually poor and often heavily infested with mice.

*Primary Lesion.* In 29 of the 35 patients primary cutaneous lesions could be readily identified. These consisted of areas of erythema and in-

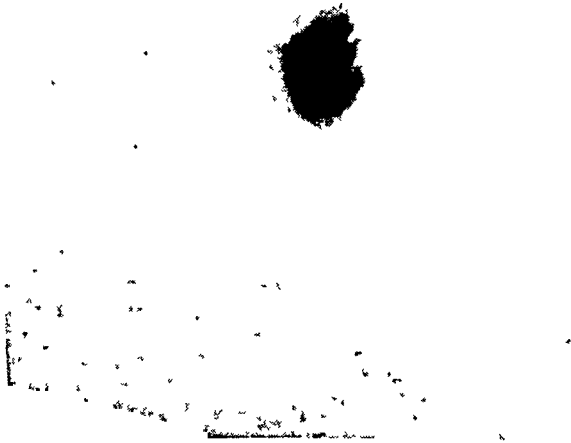


FIG. 1. A typical late primary lesion. This lesion was situated on the right upper arm of a 15-year-old boy.

duration from 1.0 to 2.5 centimeters in diameter. At an early stage the lesions exhibited a central vesicle containing slightly cloudy or opaque fluid. In older lesions this vesicle had ruptured or undergone desiccation, leaving a dark brown or black crust which closely resembled the primary eschar described in *fièvre boutonneuse*, *tsutsugamushi* disease, and occasionally in cases of Rocky Mountain spotted fever. The lesion was slightly painful and tender in a few instances, but usually it produced no local symptoms and in several cases it had not been previously recognized by the patient. A typical late primary lesion is shown in figure 1.

Twelve patients had single primary lesions on either the arms or legs. The head or neck was the site in eight others, in one of whom it was situated

just inside the right nostril. This latter individual had contracted the infection accidentally in the laboratory. Four other patients showed lesions on the back, buttock and penis. In the remaining five patients *two* primary lesions were observed and were distributed as follows: forehead and cheek; forehead and abdomen; forehead and leg; chest and axilla; and two close together on the thigh, which are illustrated in figure 2. In almost every instance the lymph nodes draining the areas where the primaries were situated were enlarged and slightly tender, but although this local lymphadenopathy was often striking in its magnitude there was never any evidence of lymphangitis.

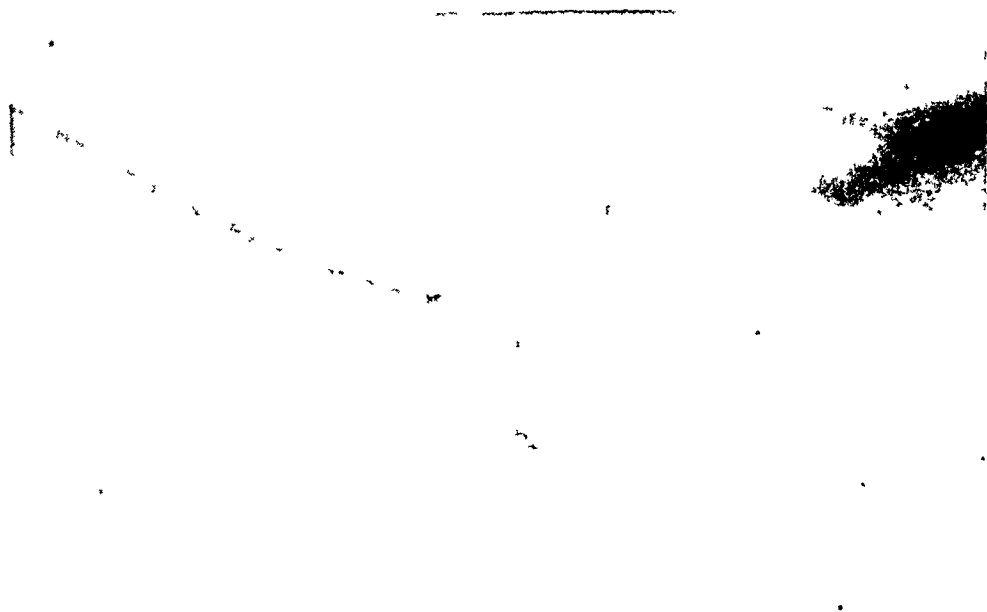


FIG. 2. Two primary lesions situated close together on the thigh of a two-year-old girl.

*Cutaneous Eruption.* The cutaneous eruption of rickettsialpox appeared from a few hours up to a week after the onset of the febrile period of the disease. In the majority of cases, however, it developed within 72 hours after the temperature became elevated, and most commonly on the second day of fever. The individual lesions varied considerably in their appearance but usually consisted of erythematous maculo-papular areas ranging from 2 to 10 millimeters in diameter (figure 3). They were discrete and generally distributed over the body surface, including the face, and in three cases they were observed on the palms and soles. In several patients the rash was either so faint, or the lesions were so sparse, as to be almost inapparent. In one patient the rash was indistinguishable from that seen in murine typhus.

The outstanding feature of the individual lesion in most cases was the development of vesiculation, although it is important to point out that occasionally no vesiculation whatever was seen. In a number of instances the vesicles appeared only as small, pin-point, opaque areas at the summits of papules. More frequently, however, the vesicles were larger and often con-

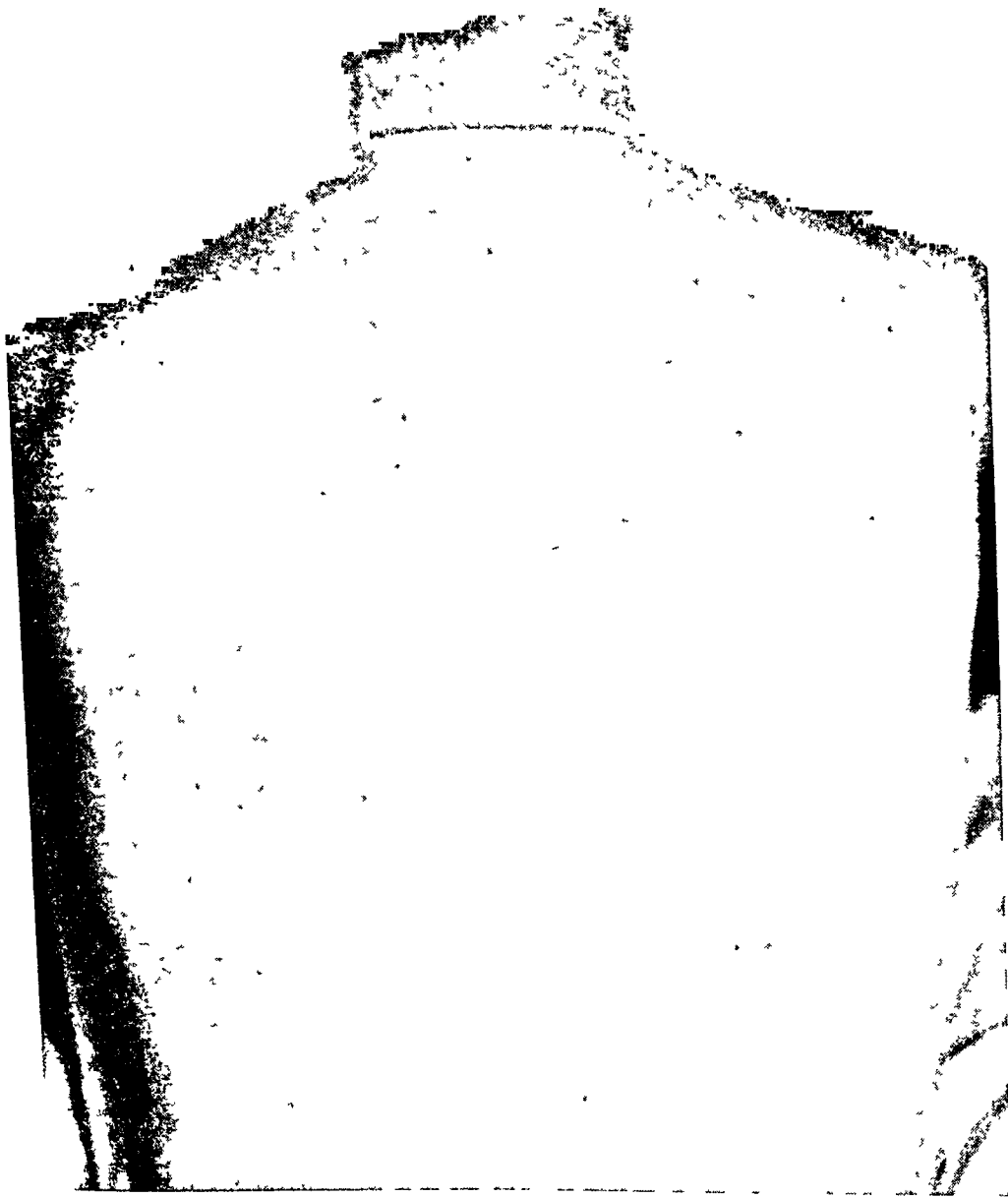


FIG 3. The typical secondary eruption of rickettsialpox in a 34-year-old man.

stituted the majority of the papule, being surrounded by a band of erythema. These latter vesicles were difficult to distinguish individually from those seen in chickenpox. The eruption was pruritic in several cases although in most patients it did not cause any discomfort and was never painful. As the eruption retrogressed blackish crusts formed at the sites of the larger vesicles.



These later became detached, leaving areas of brownish pigmentation, but residual scarring was never noticed.

In nine of the 35 cases an enanthem was seen on the mucous membranes of the oral cavity, usually on the palate. The lesions resembled those seen on the body surface but were usually more transient, sometimes being visible for less than 48 hours. The enanthem may be missed unless it is searched for at daily intervals, and it is probable that the incidence is higher than recorded in this series of patients.

*Symptoms and Physical Signs.* The chief constitutional symptoms were fever, headache, and malaise, which were present in every case. These symptoms appeared from two to seven days after the patient first noted the presence of the primary cutaneous lesion. The maximum temperature ranged from as low as 100.2° F. to as high as 105.6° F., the majority being between 102° F. and 104° F. The fever curve was of the remittent type and fell to normal by lysis, generally toward the end of the first week.

Headache was an outstanding feature and was usually severe and located in the frontal area. In two cases, however, it was mainly occipital.

Malaise was always present, often accompanied by backache and generalized muscular aching. Nearly all of the patients complained of chilly sensations and about half of them had shaking chills, sometimes accompanied by drenching sweats. Other symptoms noted occasionally were rhinorrhea, cough, sore throat, photophobia, pain on movement of the eyes, nausea and vomiting. Four patients had pain and stiffness of the neck, which were sufficiently marked in three of them to warrant lumbar puncture.

On physical examination there was ordinarily little to be found except the cutaneous eruption and the primary lesion, when present. As previously noted, the regional lymph nodes draining the site of the primary lesion were usually enlarged and tender. However, a generalized lymphadenopathy was observed in only five patients and in none of these was it striking. The spleen was palpable at the height of the disease in four patients and a mild conjunctivitis appeared in three others. Examination of the cardiovascular system was invariably negative and only one patient, an infant two years of age, had signs of pulmonary involvement. In this patient the physical examination revealed dullness and moist râles over the left lower chest posteriorly and the roentgen-ray findings were compatible with a bronchopneumonia of the left lower lobe. Unfortunately it could not be determined with certainty whether the pneumonitis was directly associated with the rickettsial infection or whether some other etiological agent was responsible.

#### LABORATORY DIAGNOSIS

The routine laboratory examinations regularly failed to disclose anything of note with the exception of the total and differential leukocyte counts. Counts were done in 28 of the 35 cases and in 21 of these there was a moderate or marked leukopenia during the acute phase of the illness with cells

ranging between 2,500 and 5,500 per cubic millimeter. Five patients had total counts from 6,000 to 10,000 and two patients had a slight leukocytosis, the maximum being 12,500 cells. The differential count was essentially normal in 22 patients and no abnormal leukocytes were seen in the stained smear. In six individuals, however, the smears showed a number of abnormal leukocytes—large mononuclear cells with vacuolated cytoplasm—similar to the peculiar cells usually seen in the blood of patients with infectious mononucleosis. Indeed, three of these patients were admitted to the hospital with a provisional diagnosis of infectious mononucleosis based in part on the hematological findings. The abnormal mononuclear cells did not tend to persist in the blood and were present for only a day or two; their significance is undetermined. Tests for heterophile antibody never showed a significantly elevated titer of sheep cell agglutinins, either during the acute illness or in convalescence.

Rickettsialpox is similar to Q fever, among the group of rickettsial infections, in that the Weil-Felix reaction is negative. Agglutinative tests with *Proteus* OX19 and OXK were done with the acute and convalescent phase serums of 13 patients and in no instance was a positive result obtained although low titers of agglutinins were observed in a few cases.

The serums of a number of patients were also tested for cold agglutinins against Group O human erythrocytes and in none were the titers significantly elevated.

Examinations of the cerebrospinal fluid in the three patients previously referred to were completely negative.

*Specific Serologic Diagnosis.* In recent years serologic methods have been developed for the precise diagnosis of rickettsial infections. The method most widely employed is the complement fixation test, using antigens prepared from rickettsiae grown in the yolk sacs of chick embryos. One type of antigen consists of washed, concentrated rickettsial suspensions from which the chick tissue has been largely removed by flocculation and differential centrifugation.<sup>11</sup> Another type is the soluble antigen which is released into the aqueous phase when saline suspensions of infected yolk sacs are shaken with ether.<sup>12</sup> This soluble antigen gives specific reactions, is easy to prepare and can be obtained from all species of rickettsiae except *Coxiella burnetii*, the causative agent of Q fever.<sup>13</sup> In performing complement fixation tests for diagnosis the principle adhered to, if possible, is simultaneously to test two serums, one obtained in the acute phase of the illness and the other in convalescence, from two to six weeks later. The demonstration of the appearance of antibody, or of a significant rise in antibody titer, in the convalescent serum, establishes the temporal relationship of the specific immune response to the illness and thereby enables a retrospective diagnosis to be made. If no acute phase serum has been obtained, as in cases where the patient is first seen after the disease has subsided, the examination of a convalescent specimen alone may still give information of diagnostic value.

Complement fixation tests were carried out with acute and convalescent phase serums from all patients in this series, with the exception of two from whom no convalescent specimens could be obtained. The antigens were of the soluble type, prepared from *R. akari* grown in chick embryos, together with similar antigens obtained from the rickettsiae of murine typhus and Rocky Mountain spotted fever.\* Serial doubling dilutions of the sera ranging from 1-8 to 1-256 were tested by a modified Kolmer technic, using two exact units of complement in the system. The period of fixation was usually one hour at 37° C., since good results were obtained under these conditions and the anti-complementary properties of the serums and antigens were much less of a problem than when fixation overnight at 4° C. was used. Some of the serums, however, were tested by the latter fixation method.

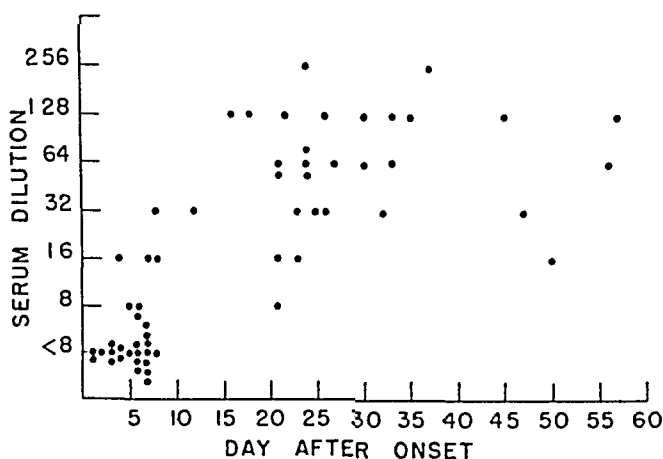


FIG. 4. A composite record of the results of complement fixation tests with rickettsialpox antigen at intervals following the onset of the disease.

Positive results were recorded as the highest dilutions of the serums that gave at least 2 plus fixation with the various antigens.

The composite results of the complement fixation tests with rickettsialpox antigen are shown in figure 4. In every case tests revealed the development of specific antibody and thereby confirmed the clinical diagnosis. A considerable degree of cross reaction was observed with the rickettsialpox and spotted fever antigens indicating a close antigenic relationship between *R. akari* and *R. rickettsii*. Indeed, in some patients the complement fixation reactions were more strongly positive with spotted fever antigen than with rickettsialpox antigen, an observation which has also been reported by Huebner and his associates.<sup>3</sup> In addition, minor cross reactions were observed occasionally with murine typhus antigen. These findings are illustrated in table 1, which shows some representative results of complement

\* The murine typhus and Rocky Mountain spotted fever antigens were generously supplied by Dr. Herald R. Cox, Director, Section of Viral and Rickettsial Research, Lederle Laboratories, Pearl River, New York.

fixation tests with all three antigens. The serological relationships of *R. akari* are of great interest and are under further study at the present time.

Complement fixation tests were also done on the serums of three patients collected 9, 10 and 15 months, respectively, after infection. Moderately elevated titers of antibody were still demonstrable in each instance, indicating that the immune response is of fairly long duration, a phenomenon that has been shown to occur in other rickettsial diseases such as murine typhus<sup>14</sup> and Q fever.<sup>15</sup> The persistence of detectable antibody for many months after all clinical signs of the disease have subsided is of some practical significance in attempting to make a long-range retrospective diagnosis in certain cases.

TABLE I

Cross Reactions in Complement Fixation Tests with Serums of Cases of Rickettsialpox

Case	Day after Onset	Rickettsialpox Antigen	Spotted Fever Antigen	Murine Typhus Antigen
R. S.	6 24	0 64*	0 64	0 0
E. M.	7 45	0 128	0 32	0 8
H. R.	1 24	0 64	0 128	0 16
L. W.	4 30	16 64	0 16	0 8
L. A.	6 21	0 64	0 128	0 0
A. W.	8 26	16 128	32 64	16 16
A. J.	4 12	0 16	8 32	0 0
H. S.	6 37	0 256	0 32	0 0

\* Figures are reciprocals of the highest serum dilutions giving at least 2 + fixation with the respective antigens.

*Isolation of the Etiological Agent.* Attempts were made to recover the etiological agent in 10 patients by inoculating blood collected early in the disease intraperitoneally into mice, guinea pigs and into the yolk sac of chick embryos. From eight of these patients *R. akari* was isolated in the mice and from one individual the organism was also isolated directly in chick embryos. No primary isolations were successful in guinea pigs. The method employed was to inject a group of 8 to 10 Swiss mice each intraperitoneally with 0.5 to 1.0 c.c. of defibrinated blood freshly collected from the patient. Blood clot triturated with sterile bacteriological broth also proved to be a satisfactory inoculum. If animals were not immediately

available the blood was frozen and stored in a cabinet refrigerated with solid carbon dioxide. We have isolated rickettsiae from such specimens at intervals up to six months after storage.

Deaths were rarely observed in infected mice following primary inoculation, but in the second week after injection the animals often appeared ill and exhibited lethargy, ruffled fur, labored breathing and anorexia. Not infrequently, however, infected mice appeared to be perfectly healthy. Regardless of their external appearance the animals were sacrificed from seven to 10 days after inoculation and examined for inguinal and axillary lymphadenopathy, increased amounts of peritoneal fluid, and hypertrophy and congestion of the spleen and liver. Any or all of these signs were found to



FIG. 5. *Rickettsia akari* in a smear of the peritoneal fluid of an infected mouse. Stained by Macchiavello's method. Note rickettsiae in the nucleus as well as in the cytoplasm of the cell. Many of the organisms are extracellular.

denote infection and rickettsiae could be easily demonstrated in smears of the spleen, liver and intraperitoneal fluid stained by the Macchiavello method. The organisms were observed lying extracellularly as well as within both the cytoplasm and the nucleus of parasitized mononuclear cells (figure 5).

The accumulation of peritoneal fluid was often striking and occasionally exceeded 2.0 c.c. in mice weighing between 15 and 20 grams.

Subsequent passage of suspensions of infected liver and spleen to fresh mice usually resulted in a fatal illness, the animals dying from 5 to 10 days after inoculation, depending on the size of the inoculum, with typical findings at autopsy. Among the eight strains of *R. akari* isolated in this manner, to date, serial passage in mice has shown some to be of relatively low

virulence while others are highly pathogenic with LD50 titers exceeding  $10^{-5}$ .

From infected mice on the primary or later passages, *R. akari* were readily transferred to chick embryos. Suspensions of liver and spleen were inoculated into the yolk sacs of seven day old embryos which were then incubated at 35° C. The embryos died from four to nine days later, depending on the size of the inoculum, and numerous rickettsiae were demonstrated in the smears of the yolk sacs stained by the Macchiavello method. Once established, the strains could be maintained indefinitely in chick embryos by serial passage. Studies of one strain have shown that its pathogenicity for mice remained unimpaired through six consecutive transfers in eggs.

### TREATMENT

Rickettsialpox is a non-fatal disease and therefore the need for specific therapy is not as urgent as it is for other rickettsial infections such as typhus and spotted fever. Nevertheless, the unmodified infection may cause severe constitutional symptoms and the patient may be acutely and uncomfortably ill for a few days to a week or more. Certain antibiotics, including streptomycin,<sup>16</sup> chloromycetin<sup>17</sup> and aureomycin<sup>18</sup> have been shown to exercise a rickettsiostatic effect in chick embryos and experimental animals, while both aureomycin and chloromycetin have recently been demonstrated to have a remarkable therapeutic action in human rickettsial infections.<sup>19</sup> We have treated one case of rickettsialpox with streptomycin in a dosage of 0.5 gm. every six hours, but the drug apparently failed to influence the natural course of the disease. More recently, two patients were treated early in the disease with aureomycin in a dose of 1.0 gm. every six hours by mouth. In each of these cases the temperature fell precipitously to normal within 24 hours, accompanied by a rapid defervescence of symptoms and fading of the cutaneous eruption. The results of aureomycin therapy in human infections with *R. akari* will be reported in more detail elsewhere.

### SUMMARY

Rickettsialpox is a novel rickettsial infection of relatively mild character which thus far has not been observed beyond the environs of New York City.

The clinical and laboratory features of the disease have been described together with means for specific serologic diagnosis and isolation of the etiological agent.

### BIBLIOGRAPHY

1. SUSSMAN, L. N.: Kew Gardens' spotted fever, New York Med., 1946, ii, 27-28.
2. SHANKMAN, B.: Report on an outbreak of endemic febrile illness, not yet identified, occurring in New York City, New York State Jr. Med., 1946, xlvii, 2156-2159.
3. HUEBNER, R. J., STAMPS, P., and ARMSTRONG, C.: Rickettsialpox—a newly recognized rickettsial disease. I. Isolation of the etiological agent, Pub. Health Rep., 1946, lxi, 1605-1614.

4. HUEBNER, R. J., JELLISON, W. L., and POMERANTZ, C.: Rickettsialpox—a newly recognized rickettsial disease. IV. Isolation of a rickettsia apparently identical with the causative agent of rickettsialpox from *Allodermanyssus sanguineus*, a rodent mite, Pub. Health Rep., 1946, lxi, 1677-1682.
5. PHILIP, C. B., and HUGHES, L. E.: The tropical rat mite, *Liponyssus bacoti*, as an experimental vector of rickettsialpox, Am. Jr. Trop. Med., 1948, xxviii, 697-705.
6. HUEBNER, R. J., JELLISON, W. L., and ARMSTRONG, C.: Rickettsialpox—a newly recognized rickettsial disease. V. Recovery of *Rickettsia akari* from a house mouse (*Mus musculus*), Pub. Health Rep., 1947, lxii, 777-780.
7. GREENBERG, M., PELLITERRI, O., and JELLISON, W. L.: Rickettsialpox—a newly recognized rickettsial disease. III. Epidemiology, Am. Jr. Pub. Health, 1947, xxxvii, 860-868.
8. GREENBERG, M.: Personal communication.
9. GREENBERG, M., PELLITERRI, O., KLEIN, I. F., and HUEBNER, R. J.: Rickettsialpox—a newly recognized rickettsial disease. II. Clinical observations, Jr. Am. Med. Assoc., 1947, cxxxiii, 901-906.  
GREENBERG, M., and PELLITERRI, O.: Rickettsialpox, Bull. N. Y. Acad. Med., 1947, xxiii, 338-351.
- ROSE, H. M.: Rickettsialpox, New York State Jr. Med., 1948, xlviii, 2266-2270.
10. ROSE, H. M.: Unpublished observations.
11. PLOTZ, H.: Complement fixation in rickettsial diseases, Science, 1943, xcvi, 20-21.
12. CRAIGIE, J.: Application and control of ethyl-ether-water interface effects to the separation of rickettsiae from yolk sac suspensions, Canad. Jr. Res., Section E, 1945, xxiii, 104-114.
13. TOPPING, N. H., and SHEPARD, C. C.: The preparation of antigens from yolk sacs infected with rickettsiae, Pub. Health Rep., 1946, lxi, 701-707.  
COX, H. R.: Specific complement-fixing diagnostic antigens for viral and rickettsial diseases, Am. Jr. Pub. Health, 1948, xxxviii, 351-360.
14. RICKARD, E. R.: Complement fixation in human sera following murine typhus, Proc. Soc. Exper. Biol. and Med., 1948, lxix, 31-34.
15. SULKIN, S. E., and STRAUSS, E.: Studies on Q fever: Persistence of complement-fixing antibodies after naturally acquired infection, Proc. Soc. Exper. Biol. and Med., 1948, lxvii, 142-144.
16. MORGAN, H. R., STEVENS, D. A., and SNYDER, J. C.: Effect of streptomycin on growth of rickettsiae in eggs, Proc. Soc. Exper. Biol. and Med., 1947, lxiv, 342-345.  
SMADEL, J. E., JACKSON, E. B., and GAULD, R. L.: Factors influencing the growth of rickettsiae. I. Rickettsiostatic effect of streptomycin in experimental infections, Jr. Immunol., 1947, lvii, 273-284.
17. SMADEL, J. E., and JACKSON, E. B.: Chloromycetin, an antibiotic with chemotherapeutic activity in experimental rickettsial and viral infections, Science, 1947, cvi, 418-419.
18. WONG, S. C., and COX, H. R.: Action of aureomycin against experimental rickettsial and viral infections, Ann. N. Y. Acad. Sci., 1948, li, 290-305.  
ANIGSTEIN, L., WHITNEY, D. M., and BENINSON, J.: Aureomycin—a new antibiotic with antirickettsial properties: Its effect on experimental spotted fever and epidemic typhus, Ann. N. Y. Acad. Sci., 1948, li, 306-317.
19. SMADEL, J. E., WOODWARD, T. E., LEY, H. L., JR., PHILIP, C. B., and TRAUB, R.: Chloromycetin in the treatment of scrub typhus, Science, 1948, cviii, 160-161.  
SMADEL, J. E., LEON, A. P., LEY, H. L., JR., and VARELA, G.: Chloromycetin in the treatment of patients with typhus fever, Proc. Soc. Exper. Biol. and Med., 1948, lxviii, 12-19.
- PINCOFFS, M. C., GUY, E. G., LISTER, L. M., WOODWARD, T. E., and SMADEL, J. E.: The treatment of Rocky Mountain spotted fever with chloromycetin, Ann. Int. Med., 1948, xxix, 656-663.

- LENNETTE, E. H., MEIKLEJOHN, G. and THELEN, H. M.: Treatment of Q fever in man with aureomycin, *Ann. N. Y. Acad. Sci.*, 1948, li, 331-342.
- COOKE, C.: Rocky Mountain spotted fever treated with aureomycin, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 885.
- ROSS, S., SCHOENBACH, E. B., BURKE, F. G., BRYER, M. S., RICE, E. C., and WASHINGTON, J. A.: Aureomycin therapy of Rocky Mountain spotted fever, *Jr. Am. Med. Assoc.*, 1948, cxxxviii, 1213-1216.
- HARRELL, G. T., MEADS, M., and STEVENS, K.: "Aureomycin," a new orally effective antibiotic, *South. Med. Jr.*, 1949, xlii, 4-13.
- SCHOENBACH, E. B.: Aureomycin therapy of recrudescant epidemic typhus (Brill's disease), *Jr. Am. Med. Assoc.*, 1949, cxxxix, 450-452.



# PULMONARY EMBOLISM: ITS INCIDENCE AT NECROPSY IN RELATION TO PERIPHERAL THROMBOSIS \*

By J. M. SPITZER, M.D., NORMAN ROSENTHAL, M.D., MURRAY WEINER, M.D., and SHEPARD SHAPIRO, M.D., *New York, N. Y.*

THE most dangerous complication of venous thrombosis is pulmonary embolism, with its mortality of about 20 per cent.<sup>1</sup> Such embolism has been reported by Barnes<sup>3</sup> to be responsible for 34,000 deaths in this country each year. Knauer<sup>2</sup> has reported fatal pulmonary embolism in 2.5 per cent of 33,558 autopsies. Hunter<sup>4</sup> found that over 50 per cent of older people confined to bed evidenced thrombosis of the deep leg veins, with pulmonary emboli from these veins accounting for over 3 per cent of all deaths.

The factors which determine whether a thrombus will or will not embolize are not fully understood. It is commonly assumed that the incidence of pulmonary embolism in any given age or disease group is a direct function of the incidence of thrombosis. If this were not so, the nature of the disorders with an altered frequency of embolization might serve as a clue to the understanding of embolization. Accordingly, a study was undertaken to determine if disease of any particular system enhanced or retarded the embolization of thrombi. This postmortem study was further stimulated by the clinical impression that the incidence of peripheral thrombosis and pulmonary embolism was surprisingly low at Goldwater Memorial Hospital. This hospital consists largely of elderly, chronically bed-ridden patients who might be considered likely candidates for more frequent thromboembolic disease.

*Material:* In this study, the postmortem incidence of embolism and thrombosis in various disease and age groups was compared. The necropsy protocols of 516 cases were studied. The first 202 of these were consecutive cases consisting of 67 females and 135 males ranging in age from 18 to 89. As will become evident in the analysis of the data, the diagnosis of Laennec's cirrhosis assumed a singular rôle. Therefore, an additional 79 consecutive autopsy protocols in which there was a final diagnosis of Laennec's (portal) cirrhosis were selected for further study. In addition, 217 non-cirrhosis protocols of selected age groups were also reviewed.

## ANALYSIS OF DATA

Table 1 showed the incidence of thrombosis to be comparatively low in the age group below 50. In the age groups beyond 50, thrombi were

\* Received for publication October 28, 1948.

From the Third (New York University) Division, Goldwater Memorial Hospital, Welfare Island, New York 17, N. Y., and the Department of Medicine, New York University College of Medicine, New York, N. Y.

found with a frequency twice as high as in the younger group.\* When analyzed by individual decades, no significant variation was found. Pulmonary emboli, on the other hand, manifested a marked statistical increase beyond 70 years of age. It should be noted that while the incidence of arteriosclerosis in the age group 60 to 69 was equivalent to that found in the older decades, the incidence of pulmonary embolism was considerably less. As was anticipated, the incidence of arteriosclerosis was found to rise sharply until age 60. Beyond this age, the incidence was too high to permit useful comparison by decades.

In table 2 the data were correlated with the pathologist's final diagnosis. Cardiac thrombosis was found with greatest frequency (28 per cent) in the cardiovascular group and peripheral thrombosis was noted in 20 per cent of the 101 cases comprising this group. In the 18 patients constituting the hepatic disease group, cardiac thrombosis occurred in five cases and periph-

TABLE I

Age	Total Number of Cases	Thrombi	Pulmonary Emboli	Atherosclerosis
Under 50	20	3 15%	1 5%	10 50%
50-59	32	11 34%	1 3%	24 72%
60-69	56	21 41%	5 9%	52 93%
70-79	58	21 40%	11 21%	56 96%
80-89	36	12 36%	8 23%	33 92%

eral thrombosis in two cases. Pulmonary embolism occurred in from 10 to 20 per cent of all disease groups with the startling exception of cases of portal cirrhosis. In the 18 cases of portal cirrhosis, there was not one instance of pulmonary embolism. No extrapulmonary embolus was discovered in the hepatic disease group with the possible exception of one doubtful case. In no other disease group analyzed were emboli so totally lacking.

The failure to demonstrate emboli in the patients with liver disease led us to examine the autopsy protocols of other cases bearing a final diagnosis of Laennec's cirrhosis. Seventy-nine additional consecutive cases of Laennec's cirrhosis examined at autopsy were analyzed. In 17 of the 79

\*This report is based on autopsies conducted according to the routine established in the laboratory. It is probable that if special dissections of the lower limbs were made the incidence of peripheral thrombosis would be higher than is recorded in this paper. Nevertheless, since the necropsies were all performed according to the same technic, a comparison of incidence in the different groups is valid. In each case dissection of the pulmonary arteries was carried out in the same routine manner.

cases, cardiac thrombi were found. Peripheral thrombosis was present in nine cases. This compares favorably with the figures obtained among the 18 cases of liver disease presented in table 2. In one case, a non-embolic thrombus was discovered in the pulmonary artery but again we failed to find

TABLE II

Disease Group		Total Number of Cases	Incidence of					Athero- sclerosis
			Thrombosis		Embolism			
			Cardiac	Peripheral	Pulmonary	Other	Doubtful	
Cardiovascular	Number Per cent	101	38 38%	20 20%	15 15%	20 20%	2 2%	92 92%
Hepatic	Number Per cent	18	5 28%	2 11%			1 6%	14 77%
Renal	Number Per cent	29	4 14%	3 10%	4 14%	3 10%	1 4%	25 88%
Respiratory	Number Per cent	51	6 12%	3 6%	5 10%	4 8%	2 4%	45 90%
Neurological	Number Per cent	46	6 13%	6 13%	9 20%	5 11%	1 2%	38 84%
Malignancy	Number Per cent	45	5 11%	7 16%	6 13%	6 13%		35 71%
Additional Cases of Hepatic Disease								
Hepatic	Number Per cent	79	17 21%	9 11%	0	1 5%	0	16 80%

a single instance of pulmonary embolism in the 79 cases of portal cirrhosis. One case revealed an extrapulmonary embolus. Combining the 18 cases presented in table 2 with the additional 79 of table 3 we find that in 97 cases of portal cirrhosis no pulmonary emboli were uncovered.

## DISCUSSION

It is the common belief that thrombosis and embolism are parallel phenomena. Our data reveal two significant findings which fail to support this concept: (1) The absence of pulmonary embolization in 97 cases of cirrhosis of the liver regardless of age group, and (2) A sharp increase in the incidence of emboli to the lungs in patients after 70 years of age. In both groups peripheral thrombosis was found with about equal frequency.

The conditions responsible for the development of intravascular thrombosis appear to be inadequate to explain the variable incidence of pulmonary thromboembolism as revealed by the above data. The blood coagulation

mechanism is usually disturbed in chronic liver disease.<sup>5</sup> It is unlikely that the prothrombin time delay frequently seen in cirrhosis of the liver could inhibit embolization without preventing peripheral thrombosis. In the older age groups the blood has also been found to be hypocoagulable<sup>8</sup> and liver function tests in the aged have frequently been demonstrated to be abnormal even in the absence of clinically demonstrable liver disease.<sup>5</sup> Nevertheless the data show a striking increase in the incidence of pulmonary thromboembolism beyond 70 years of age. We are led to conclude, therefore, that factors other than simple hypocoagulability may influence the incidence of pulmonary embolism.

This belief is strengthened further by the observation that certain cases of the migratory type of thrombophlebitis seem almost never to yield emboli while others clinically indistinguishable from the former variety, are frequently accompanied by pulmonary embolization. The first type of migratory thrombophlebitis may continue for many months, manifesting frequent fresh lesions without endangering the host with emboli to the lungs.<sup>6</sup> In the latter, pulmonary embolism may occur with startling frequency during the course of the disease.<sup>7</sup> These two types can be further distinguished by their response to anticoagulants. The embolizing type can be controlled by adequate anticoagulant therapy while the non-embolizing type sometimes cannot.

#### SUMMARY AND CONCLUSIONS

In 184 consecutive miscellaneous cases, excluding liver disease, the incidence at necropsy of pulmonary embolism was 14 per cent.

In 97 instances of portal cirrhosis, no pulmonary emboli were found. The incidence of cardiac and peripheral venous thrombosis in these 97 cases of liver disease was not significantly different from that of the miscellaneous group.

Since decreased coagulability of the blood is accompanied by reduced embolization in some instances (cirrhosis of the liver) and by increased embolization in other instances (aged patients), factors other than changes in coagulability of blood must be sought to explain the occurrence of pulmonary embolism.

*Acknowledgment:* The authors wish to thank Dr. Julius Rosenthal for permission to study the protocols of the cases described in this paper and to use the material for publication.

#### BIBLIOGRAPHY

1. JORPES, J. E.: Heparin in the treatment of thrombosis, 2nd Ed., 1946, Oxford University Press, London, page 149.
2. KNAUER, J. G.: Acute cor pulmonale: discussion of literature and report of case successfully treated with oxygen, Bull. Am. Acad. Tuberc. Phys., 1939, iii, 36.
3. BARNES, A. R.: The problem of pulmonary embolism, West. Jr. Surg., 1942, 1, 551.

4. HUNTER, W. C., SNEEDEN, V. D., ROBERTSON, T. D., and SNYDER, G. A. C.: Thrombosis of deep veins of leg: its clinical significance as exemplified in 351 autopsies, *Arch. Int. Med.*, 1941, lxviii, 1.
5. UNGER, P. N., WEINER, M., and SHAPIRO, S.: The vitamin K tolerance test, *Am. Jr. Clin. Path.*, 1948, xviii, 835.
6. HOMANS, J.: *Circulatory diseases of the extremities*, 1939, Macmillan Co., New York.
7. FLOOD, E. P., REDISH, M. H., BOCIEK, S. J., and SHAPIRO, S.: Thrombophlebitis migrans disseminata: report of case in which gangrene of breast occurred. Observations on therapeutic use of Dicumarol (3,3' methylenebis-(4-hydroxycoumarin)), *N. Y. State Jr. Med.*, 1943, xliii, 1121.
8. SHAPIRO, S.: Unpublished data.

# CHEST X-RAY SURVEYS IN GENERAL HOSPITALS, A CRITICAL REVIEW \*

By KATHARINE R. BOUCOT, DAVID A. COOPER, F.A.C.P., E. WAYNE MARSHALL, and FRED MACD. RICHARDSON, *Philadelphia Pennsylvania*

ROENTGENOGRAPHIC chest surveys of general hospital populations are fairly recent innovations. In 1936, Hodges<sup>4</sup> reported a chest x-ray survey of 1101 admissions to the University of Michigan Hospital. He found roentgen evidence of intrathoracic lesions in 90, or 8.1 per cent of those patients. Examination of their subsequent hospital records revealed 14 instances in which pulmonary pathology found on the survey films had not been recognized clinically. This represented an incidence of 1.5 per cent. Also in 1936, Pohle et al.<sup>8</sup> reported 1460 hospital admissions with normal lungs on physical examination. In 34, or 2.3 per cent of this group, x-ray evidence of pulmonary tuberculosis was present, and in four, or 0.3 per cent, active reinfection tuberculosis was suspected. In 1940, Plunkett and Mikol<sup>7</sup> reported x-raying 4853 admissions to 14 general hospitals in upstate New York and in 128, or 2.6 per cent, evidence of reinfection tuberculosis was found. No clinical data were presented in this series.

During the past 10 years, marked technical improvements have made available a miniature chest photofluorographic technic which was widely used by induction centers, the armed services, and large industrial plants during the war. With this background of previous experience, the United States Public Health Service and local health agencies have sponsored mass chest surveys in various localities throughout the United States.

The first report in the literature on the use of photofluorography in hospital surveys appeared in 1941. Douglas and Birkelo<sup>2</sup> reported examining 4727 prospective mothers on 4 by 5 film. In 29, or 0.61 per cent, roentgen evidence of active tuberculosis was discovered.

The first use of photofluorography as a *routine* hospital procedure appeared in April, 1942, when Hodges<sup>5</sup> analyzed 7841 patients admitted to the University of Michigan Hospital during a four month period. He found that 732, or 9.3 per cent, required more comprehensive x-ray study. Again there was no report of clinical follow-up on the group.

In 1945, Scatchard and Duszynski<sup>9</sup> reported the results of a chest survey made on 1832 admissions to the Edward J. Myer Memorial Hospital of Buffalo during the two and one-half summer months of 1944. Of these, 36, or 1.4 per cent, were found to have previously unsuspected pulmonary tuberculosis. Ten of the 36 cases had either been x-rayed previously and found negative or had not been x-rayed on previous admissions. The remaining 26 had never before been seen at the hospital. Further, in 1107 of these

\* Received for publication March 30, 1948.

patients previously known to the hospital, the prevalence of unsuspected tuberculosis was 1.1 per cent in contrast to a prevalence of 3.6 per cent in the 725 individuals admitted without ever having had previous contact with the institution. These authors give suggestions for a suitable installation and stress the importance of having the unit operate between 6 p.m. and 10 p.m.

Hanser and Dundon<sup>3</sup> in 1945 reported the examination at the University Hospital in Cleveland of 1000 asymptomatic hospital employees on both 14 by 17 and 4 by 5 films. Twenty-one minimal lesions of pulmonary tuberculosis were found, an incidence of 2.1 per cent, and four errors were made in the first reading of the miniature films.

The American Hospital Association<sup>1</sup> in coöperation with the United States Public Health Service and the National Tuberculosis Association advocates for all patients entering clinics and hospitals the routine use of chest x-rays as a service comparable to the routine blood Wassermann examination.

In 1946, W. P. Shepard, the President of the National Tuberculosis Association, commented as follows: "No well run hospital would admit a case of typhoid fever without instituting proper isolation. Today tuberculosis is more common than typhoid fever, it is more elusive, often unrecognized, and is contagious. Admitted unknowingly, it is a menace to the patient, hospital personnel, other patients, and the public. Admitted knowingly, it is easy to isolate, the patient's proper care is assured, and the public is protected. Routine chest x-rays of all admissions is a feasible and practical procedure."

In the monograph, "The Management of Tuberculosis in General Hospitals," published in 1946 by the Council on Professional Practice of the American Hospital Association, it is stated that in new hospital admissions "residual signs of inactive tuberculous lung infection are seen in 10-20 per cent" while "significant tuberculosis (reinfection type) has been found in 1.5 to 4.3 per cent."

Little information can be gleaned as to follow-up procedure and ultimate results in these hospital surveys. No follow-up study of a hospital x-ray survey was found in the literature. However, Peterson,<sup>6</sup> in 1946, reported a one year hospital survey in which all new admissions to the Minneapolis General Hospital had been Mantoux tested. Positive reactors had been x-rayed and those with significant findings had been carefully followed. The present neglect of follow-up planning is reflected in the absence from the literature of appropriate emphasis on this essential aspect of survey work.

In December, 1947, an effort was made to study the current effectiveness of hospital surveys in the Philadelphia area. An analysis was undertaken of the four 70 mm. photofluorographic units operating at Philadelphia General Hospital and at three teaching hospitals—Temple, Jefferson, and Hahnemann. These four units were analyzed with the following points in mind: (1) location of the unit, (2) its lay-out, (3) procedure, (4) staff, (5) record-keeping, and (6) follow-up.

1. *Location.* Three of the four units were well located adjacent to receiving wards. The fourth unit was adjacent to the entrance for private patients and visitors.

2. *Lay-out.* Not one of the four units had a suitable lay-out. All four had inadequate space and none had a waiting room. Two units had no dressing rooms, one unit had two, both of which were poorly ventilated, and the fourth had three cubicles. Only one unit had its own developing room and that room was so small that the dryer had to be placed where it interfered with the free access of patients and technicians to the unit itself. It is apparent that these survey units had been set up in odd available space rather than as carefully planned adjuncts to the admission departments.

3. *Procedure.* No adequate system insured that all admissions report to the unit, but arrangements at one hospital were such that no patient was discharged without having received a photofluorogram. Two units arranged for the technicians to receive a daily list of admissions against which that day's photofluorograms were checked. An effort was then made to have those missed on admission report to the unit. However, by the time this list reached the wards, some of the cases were unable to be moved. No unit operated around the clock nor over week ends. No unit operated on definite shifts to cover evening admissions.

Photofluorograms were developed and read daily at three of the four units. Reports from these units were promptly appended to hospital charts. At the other unit, the system was uncertain, the impression being gained that film rolls were cut when sufficient exposures had been made and read when some member of the x-ray department could be found who was not too busy to read them.

Film-reading was done at one unit by a part-time certified roentgenologist reading daily the films taken the previous day. At a second unit four Fellows in Roentgenology took turns at daily film-reading. Films at the other two units were read by any one of the roentgenologists available at the time the films were developed. At one unit reports were sent to the wards within 24 hours of the film-reading. At a second unit the photofluorograms were stapled to the reports and these sent to the wards promptly. At neither of the other two units was there a definite system though one of these made a charge of \$1.00 per photofluorogram for both private and ward patients. The roentgenologist in charge of this unit explained that ward cases could receive reductions in this as in other charges by consulting the Social Service Department. No other unit made any charge for photofluorographic services.

4. *Staff.* The largest hospital, with 53 average daily admissions, had two full-time registered technicians and a full-time clerk operating the unit, a clerk and a secretary full-time at the unit office, a nurse and a nursing supervisor full-time for follow-up, a certified roentgenologist part-time for daily film-reading, and a part-time chest specialist as supervisor.



The next best staffed unit was in a hospital with 37.5 average daily admissions. It had one full-time unregistered technician and a second registered technician part-time. This unit was under the supervision of a Fellow in Roentgenology, as were the remaining two.

A third unit, in a hospital with 45 average daily admissions, alternated technicians from the x-ray department.

The fourth unit was operated by a stenographer who had been trained to take films. In her absence, the hospital doorman took them. This hospital had 35 average daily admissions.

There was no other personnel for record-keeping or follow-up at any of the last three described units.

5. *Record-keeping.* At the largest of the four hospitals, a master file was kept in which there was available a report on every x-ray ever taken. In addition, a "significant" file was maintained in which duplicate I.B.M. cards were filed with the 70 mm. photofluorograms and their readings plus follow-up correspondence. A ledger was maintained in which all significant cases were entered. It provided space for a five-year follow-up on each. The nurses kept a chronological file for follow-up of these cases.

At a second unit a ledger was kept in which daily entries were made of names, type of film taken, 70 mm. reading and subsequent 14 by 17 reading. However, no further follow-up was maintained. This unit also had a master file and a duplicate file of significant cases.

The other two units maintained no record-keeping system whatever so that there was no information available as to the number of photofluorograms taken on admissions. The roentgenologist in charge of one of these units "thinks" that 80 per cent of the photofluorograms were taken on out-patients. At the other unit, the resident "guessed" that a total of 20 to 30 individuals per day were processed.

No unit had available data on the time interval between admission and photofluorography and none kept a running record of percentage of admissions x-rayed.

6. *Follow-up.* Only one unit maintained a staff for follow-up of cases. At this institution two full-time nurses and one part-time chest specialist were kept busy. Hospital charts were examined and diagnostic procedures checked. Where data were inadequate the responsible service was notified. Because personnel was insufficient, emphasis was placed on those cases read as "probably active," and while this program was theoretically excellent, in practice the patient had often left the hospital before follow-up revealed inadequate clinical studies. However, at this unit the inadequacies were recognized and a definite effort is being made to correct the shortcomings. No statistical report is yet available from this unit on the number of tuberculous admissions to wards other than the tuberculosis ward.

One of the other units made an analysis in January, 1948, of photofluorograms taken over a six-month period. This analysis was based on 14 by 17 retakes only. Of the 8992 individuals x-rayed at this photofluoro-

graphic station, 14 by 17 retakes were subsequently made on 416 of the 1257 individuals read as having significant survey findings and on 261 of the 7442 negative cases. The study revealed that, of the 261 cases read "negative" by survey who incidentally had subsequent 14 by 17 films, 50, or 19.1 per cent, had pathology. Of these 50, only 23 of the retakes were chronologically sufficiently close to the survey film to be considered survey errors. Of the 416 retakes on survey cases thought to reveal significant pathology, the survey impression was confirmed in 290 and altered in 126. There was no organized clinical follow-up.

As far as could be determined no follow-up procedures were in practice at the remaining two units.

### DISCUSSION

Although hospital surveys are widely advocated, it appears that their ultimate purpose and fundamental philosophy are not clearly appreciated. The primary purpose of hospital chest surveys is not diagnostic, but is the detection of infectious tuberculosis in order to protect hospital personnel and other patients. This achievement is accomplished only by prompt diagnosis with isolation and appropriate treatment of cases uncovered by survey. If properly conducted, surveys of this type become an important adjunct to the tuberculosis control program of the community.

The concept of surveys as screening processes is of the greatest importance. Such a concept suggests that a significant percentage of cases whose films are read as "probably tuberculous" should ultimately prove to be non-tuberculous. No film should be read as revealing non-tuberculous pathology in a patient who is subsequently proved to have tuberculosis. This is one way of stating that a properly read hospital survey should be "overread" from the viewpoint of tuberculosis. Such an approach requires considerable indoctrination of survey film readers.

If hospital surveys are to be effective, a very high percentage of patients must report for photofluorography *at admission*. It is obvious that x-ray at discharge cannot protect contacts and often does not even lead to accurate diagnosis and therapy for the patient himself, viz. the following case report:

A 37-year-old white female, a private patient admitted in active labor March 31, 1947, received a 70 mm. photofluorogram at discharge 10 days post-partum. The film was read as revealing bilateral tuberculosis. The report was sent to her obstetrician who advised the patient to consult a chest specialist. The patient failed to follow this advice. On February 9, 1948, ten months post-partum, a 14 by 17 film taken because of 102° temperature, emaciation, dyspnea, etc., revealed far advanced tuberculosis with bilateral giant cavitation and soft infiltrations throughout the balance of both lungs. The baby was found to have an active tuberculosis at the right base, the husband to have a minimal lesion of indeterminate activity and a maid's film was read as suspect.

This case of active tuberculosis had been in the Maternity Division for 10 days undiagnosed and unisolated. Photofluorography at discharge had

not assisted in the protection of hospital personnel nor contacts. It did not provide a reason for clinical study which would have resulted in diagnosis. Had a positive sputum been obtained during hospitalization, the case would have been reported to the Municipal Division of Tuberculosis and follow-up would have been assured.

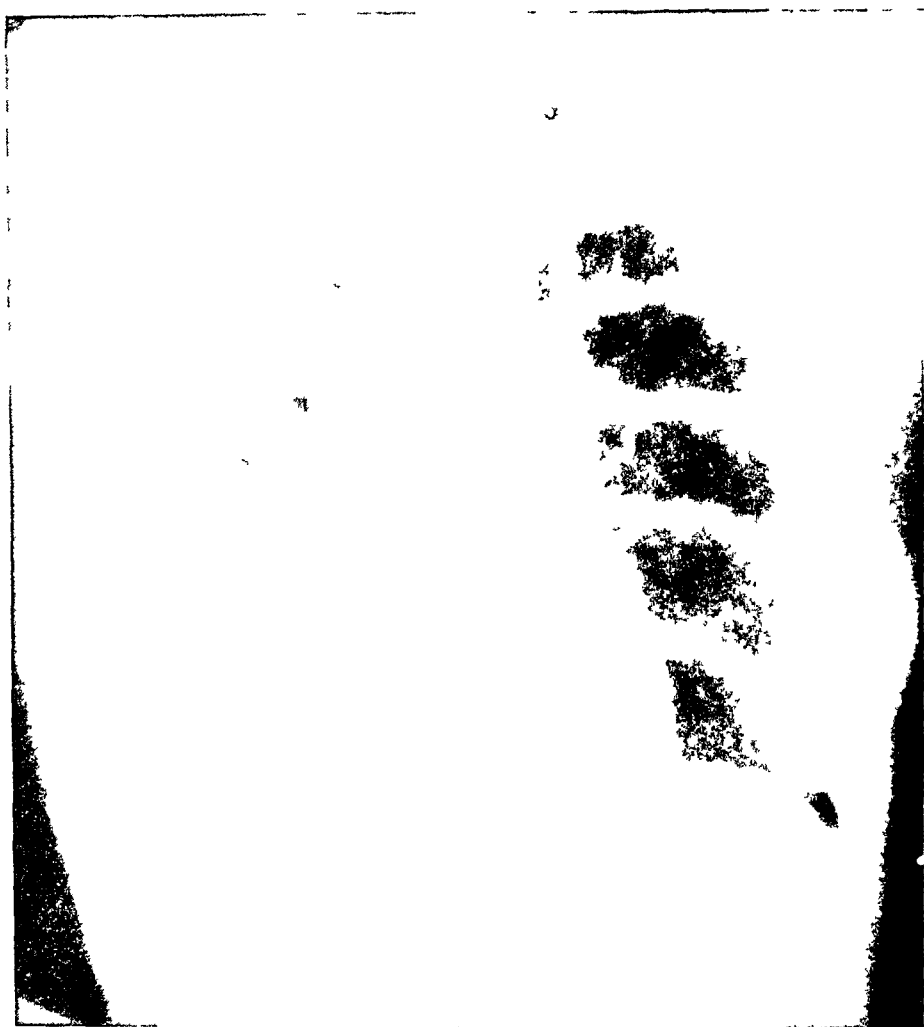


FIG. 1. A G, 37, white female, a private patient admitted in active labor on March 31, 1947, received a 70 mm. photofluorogram on April 10, 1947, at discharge 10 days post-partum which revealed moderately advanced tuberculosis with infiltrations upper halves of both lung fields.

It is apparent that some types of patients cannot be x-rayed on admission—women admitted in active labor, critically ill patients, certain accident cases, children too young, and psychotic patients too disturbed to coöperate. However, the hazards presented by such patients can be minimized by a suitable routine.

An analysis of admissions at the largest of the four hospitals revealed the fact that about 50 per cent of admissions were made during hours when the

unit was not in operation. At this hospital, during October, 1947, 1011 individuals were admitted during hours when the unit was closed. Of these 495 were too ill to report to the unit at the time they were subsequently sent for. This suggests that an important reason for failure to x-ray all admissions lies in the fact that the unit was not open around the clock.



FIG. 2. A. G., on February 9, 1948, ten months post-partum, a 14 by 17 film taken because of 102° temperature, emaciation, dyspnea, etc., revealed far advanced tuberculosis with bilateral giant cavitation and soft infiltrations throughout balance of both lungs.

One of the four units had a satisfactory follow-up program but even this was not fully effective in actual practice. It is obvious that, in the setting up of these four units, provision was made primarily for the taking and reporting of films. Record-keeping was seriously inadequate at all four units so that it was not possible to evaluate the real service rendered by these units to their respective hospitals and to the community.

## RECOMMENDATIONS

1. Photofluorographic surveys in general hospitals should be inaugurated as part of an integrated hospital tuberculosis control program rather than as ends in themselves. While the taking and reading of photofluorograms quite rightly belongs under the jurisdiction of the X-ray Department, the follow-up belongs under the Department of Chest Diseases.



FIG. 3. Baby G., 10 months old, on February 12, 1948 was found to have an active tuberculosis at the right base.

2. The taking, processing, reading and reporting of photofluorograms should be carried out within 24 hours. However, these procedures represent only the beginning of the survey work. A follow-up staff—medical, nursing, secretarial, and social service—is as necessary to an effective hospital chest survey as are the photofluorographic unit, developing room, technician, and roentgenologist. Provision for such personnel should be made when the program is set up.

3. A periodic check is necessary to be sure that all patients are being referred for photofluorograms. Responsibility for referral of admissions

and out-patients to the unit should be placed at the admission desk and the central Out-Patient Department registration desk. Some device for conspicuous marking of admission and clinic cards should be used in order that no patient be admitted to the ward, private room, or to a clinic without having received a photofluorogram. At the most successful unit studied such a

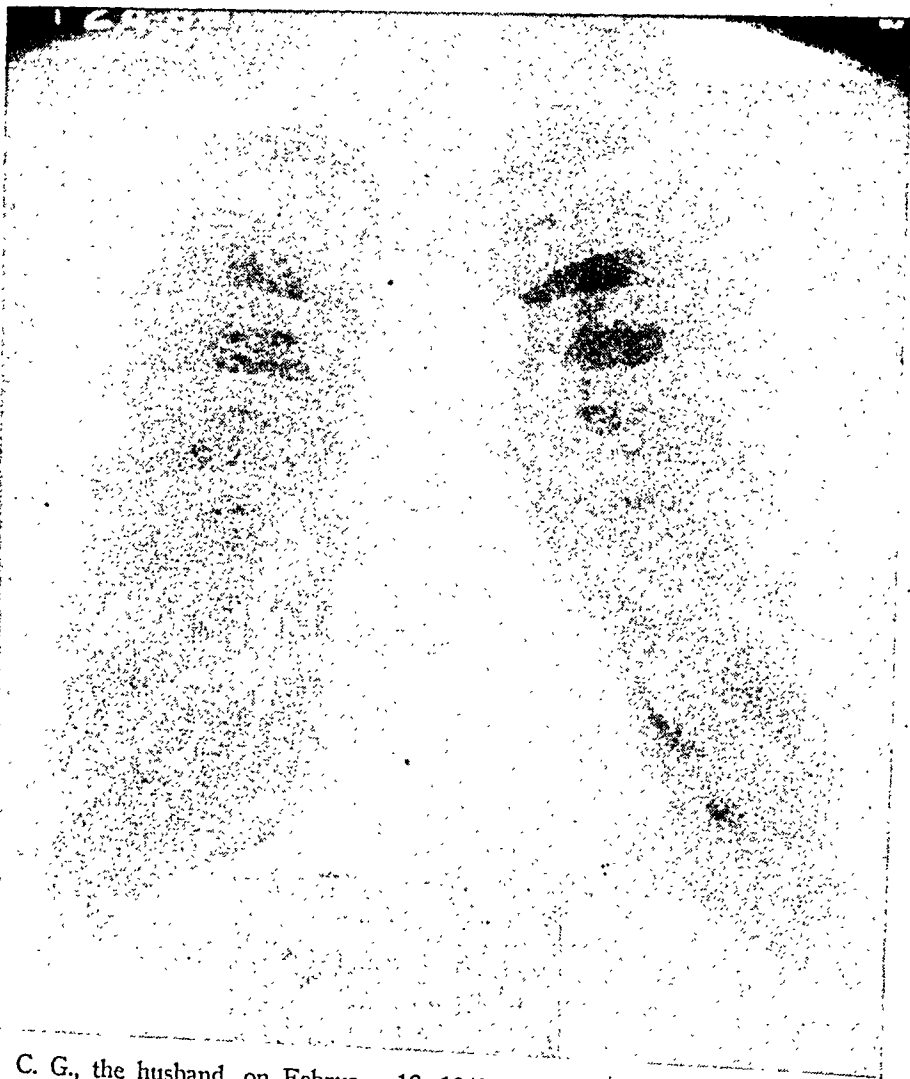


FIG. 4. C. G., the husband, on February 12, 1948 was found to have a minimal lesion of indeterminate activity at the left apex and first interspace.

device consisted of a 3.5" by 4.25" hollow "X" stamped in bright green directly over the admission or clinic card. This does not interfere with reading the data over which it is stamped.

4. Provision should be made for the taking of photofluorograms around the clock seven days a week. It is not necessary that a registered technician be on duty nights and weekends. A system should be set up for inclusion within the program of those patients who cannot be x-rayed on admission:

a. Prenatal cases and individuals scheduled for operations of election should be referred to the unit before admission.

b. Accident cases, patients having had emergency operations and children too young to coöperate should be sent via stretcher to the regular x-ray department.

c. Those cases too ill to have had photofluorograms or x-rays in the regular department should have special studies for tubercle bacilli if sputum be available.

5. The hospital office should be instructed not to discharge any patient who has not had a photofluorogram. However, constant vigilance must be exercised to obviate the necessity for referring any significant percentage of patients at discharge. The uncovering of tuberculosis at this point does not protect the patient nor his hospital contacts. Good public health practice makes it mandatory that proper follow-up be assured on these patients as well as those surveyed on admission or during hospitalization.

6. Correlation of subsequent clinical reports with survey findings should be routine and prompt, providing a valuable source of material for medical and nursing teaching.

*Note:* Since the preparation of this paper, the authors have become increasingly aware of the value of chest surveys as case-finding procedures for pulmonary neoplasms. Awareness of this aspect significantly enhances the contribution made by routine x-raying of hospital populations.

#### BIBLIOGRAPHY

1. American Hospital Association Council on Professional Practice, manual on The Management of Tuberculosis in General Hospitals—Patients, Staff, Employees, 1946.
2. DOUGLAS, B. H., and BIRKELO, C. C.: Screening for tuberculosis in a civilian population by fluorography, *Ann. Int. Med.*, 1941, xv, 853.
3. HANSER and DUNDON: Miniature chest fluorography, *Am. Jr. Roentgenol.*, 1945, liv, 470.
4. HODGES, F. J.: The medical and economic advantages of roentgenographic chest survey of all hospital admissions, *Ann. Int. Med.*, 1936, ix, 1639.
5. HODGES, F. J.: Fluorographic examination of the chest as a routine hospital procedure, *Radiology*, 1942, xxxviii, 453.
6. PETERSON, W. E.: Report of a one year survey of a diagnostic tuberculosis service in a general hospital, *Lancet*, 1946, lxvi, 118.
7. PLUNKETT, R. E., and MIKOL, E. X.: Unrecognized tuberculosis in general hospitals, *Am. Rev. Tuberc.*, 1940, xli, 381.
8. POHLE, E. A., PAUL, L. W., and OATWAY, W. H., JR.: Routine roentgen examinations of the chest of patients admitted to the State of Wisconsin General Hospital during a three-month period, *Radiology*, 1936, xxvi, 480.
9. SCATCHARD, G. N., and DUSZYNSKI, D. O.: Miniature chest x-ray films in general hospitals, *Jr. Am. Med. Assoc.*, 1945, xxvii, 746.

# CASE REPORTS

## DEATH DUE TO PARATHION, AN ANTICHOLINESTERASE INSECTICIDE \*

By DAVID GROB, M.D., WILLIAM L. GARLICK, M.D., GEORGE G. MERRILL, M. D.,  
and HENRY C. FREIMUTH, Ph.D., *Baltimore, Maryland*

THE introduction in recent years of anticholinesterase (antiChE) compounds as insecticides has led to problems arising from their toxicity for man. The antiChE compound most widely used at the present time is parathion (p-nitrophenyl diethyl thionophosphate).<sup>1</sup> This anticholinesterase was introduced by the Germans and is now manufactured in this country, chiefly for use as an insecticide in agriculture, under such names as "Geigy Parathion," "Lethalaire G-54 Parathion Aerosol," "Chipman Parathion," "P. A. R. Parathion," "Phos Kit Parathion," "Paradust Parathion," "Dow Parathion," "Vapophos Parathion," "Penphos Parathion," "Aphamite Parathion," "Parathion Insecticides," "Genithion Parathion," "Edco 15 Parathion," and "Niran (Parathion)." Studies performed following the administration of parathion to experimental animals have shown that most of the pharmacological properties of this compound can be explained in terms of its antiChE action.<sup>2, 3</sup>

Detailed studies of the effects in man of other esters of phosphoric and pyrophosphoric acid which are potent antiChE agents, such as di-isopropyl fluorophosphate (DFP) and tetraethyl pyrophosphate (TEPP, which is also employed as an insecticide), have shown that these esters produce muscarine-like, nicotine-like, and central nervous system effects.<sup>4-8</sup> Because the inhibition of cholinesterase (ChE) enzymes by DFP is irreversible, and by TEPP and parathion only partly reversible, the effects of these compounds are prolonged and cumulative. Until the ChE enzymes of the tissues have been restored, subjects who have been exposed to these compounds remain susceptible to the effects of any subsequent exposure, which may be by any route, including absorption from the skin, respiratory tract, conjunctivae, gastrointestinal tract, or following injection.

The following case report is that of a man who died after repeated exposure to the insecticide, parathion, and who manifested the characteristic cholinergic symptoms and changes in ChE activity attributable to an antiChE agent.

### CASE REPORT

A. N., a white male aged 35, was employed as a mixer of liquid parathion (97 per cent pure) and ataclay (a clay powder) to produce a clay dust with parathion

\* Received for publication August 16, 1949.

Work was performed in part under a contract between the Medical Division, Chemical Corps, U. S. Army, and the Johns Hopkins University.

From the Department of Medicine, Johns Hopkins University and Hospital, the Department of Surgery, Mercy Hospital, and the Office of the Chief Medical Examiner, Baltimore, Maryland.



adsorbed in concentration varying from 15 to 34 per cent. The resulting product is marketed and is used as an insecticide after dilution with clay to 1 to 2 per cent, or with water to 0.06 per cent, parathion. This work exposed the patient to liquid parathion and to parathion adsorbed on ataclay. He had been employed from February 21 through March 11, April 21 and 22, and from May 2 through May 6. He wore a carbon filter respirator, protective goggles, rubber gauntlets, hip length rubber boots, rubber apron, and protective coveralls, which did not, however, completely cover the arms and neck. There is no indication that he had any symptoms prior to May 6. On May 6 the concentration of parathion in the ataclay was increased from 25 to 34 per cent. (The saturation point of parathion on ataclay under standard conditions is approximately 40 per cent.) On the same day there was an increase in the atmospheric temperature and humidity. The patient worked from 3 p.m. to 7:30 p.m., when he stopped to have supper. He removed all his protective clothing except the boots and washed his hands thoroughly. The dining room and food were in a separate part of the plant from that in which parathion was handled. At 8 p.m., 10 minutes after eating, he became nauseated and then had the desire to defecate. Before he could reach the toilet, he developed abdominal cramps accompanied by vomiting, tenesmus and involuntary defecation. This continued during the next half hour, during which the patient also began to have profuse sweating, constant giddiness, headache, blurring of vision, restlessness, and anxiety. Muscular fasciculations appeared in the tongue and eyelids, and there was some generalized muscular weakness.

He was admitted to the hospital two hours after the onset of symptoms. Physical examination revealed a well developed 35 year old white man who had walked into the hospital despite moderately acute distress from the symptoms described above. He was tense, anxious, and tremulous, but rational and well oriented. He was sweating profusely, and there was excessive salivation. Speech was somewhat slurred. There was some difficulty forming words, and repetition of the last word or syllable. The pupils were pin-point, and the fundi could not be seen. Respirations were normal, at 16 per minute, and the lungs were clear. The heart was normal to percussion and auscultation. The pulse rate was 92 per minute, and the blood pressure 152/96 mm. of mercury. (The preemployment blood pressure had been 100/70, on February 20.) On admission, muscular fasciculations were observed in the tongue and eyelids, and there were irregular jerking movements of the eyes. Shortly afterward the muscular fasciculations became generalized and were very marked. There was a moderate degree of generalized muscular weakness. Tendon reflexes were normal, and there were no abnormal reflexes. No abnormality of sensation was detected.

Forty minutes after admission, the patient gradually lapsed into coma. Tendon reflexes and response to painful stimuli disappeared. Following the development of coma, repeated generalized convulsions occurred. Between convulsions the respiration was Cheyne-Stokes, except when a mixture of 5 per cent carbon dioxide and 95 per cent oxygen was administered. There was no gross evidence of bronchoconstriction, but there did appear to be excessive bronchial secretion. Otherwise the lungs remained clear. The blood pressure rose from 152/96 to 186/100. There was no evident anoxia or carbon dioxide retention to account for this rise in the blood pressure. There was frequent urinary and rectal incontinence, with watery stools. Gastric aspiration yielded 500 c.c. of brownish fluid having the mercaptan-like odor of parathion.

One pin-point pupil was slowly and incompletely dilated by the local instillation of one drop of 1 per cent atropine sulfate every 15 minutes for one hour. Examination of the fundus at that time revealed moderate elevation of the optic disc of about 2 diopters. Half an hour later the pupil returned to pin-point size, and the fundus could no longer be visualized.

The patient was treated with atropine sulfate, 0.6 mg. being injected intramuscularly four times during the first hour. This resulted in diminution of the excessive sweating, salivation, and bronchial secretion. Two hours later he received another injection of 0.6 mg. atropine sulfate. He was given a continuous infusion of saline and glucose. During his first convulsion he was given 140 units of curare intravenously over a period of three minutes. This diminished the severity of the convulsive movements, but did not prevent their recurrence. The curare immediately abolished the muscular fasciculations. He was given a second injection of curare (100 units) about half an hour after the first injection.

The patient remained comatose and areflexic for four hours. Then, seven hours after the onset of symptoms, he began to respond again to painful stimuli, and tendon reflexes could again be elicited. The pupils became less pin-point, and some response to light was obtained. Coincident with this improvement the blood pressure gradually fell from 186/100 to 150/80. One hour after the return of reflexes and of response to painful stimuli the patient regained consciousness, spoke a few words and appeared to be rational and oriented. He stated that vision in both eyes was blurred, and that he had difficulty focussing. During the next two hours he appeared to be improving gradually, becoming more alert and speaking more easily. However, shortly thereafter, 10 hours after the onset of symptoms, respiration became shallow, rapid, and labored, and the pulse unobtainable. Fifteen minutes after this change was noted the patient died.

#### AUTOPSY FINDINGS

Postmortem examination, performed four hours after death, revealed only diffuse vascular engorgement throughout the body, with widespread capillary dilatation, edema, and hyperemia of all the organs, including the lungs, liver, spleen, kidneys, and brain. The brain was edematous, and there was an increased amount of clear cerebrospinal fluid in the ventricles and subarachnoid space, as well as a "pressure cone." There was a slightly increased amount of mucus in the trachea and bronchi. These findings are in general similar to those that were observed after a death attributable to neostigmine methyisulfate.<sup>9</sup>

TABLE I

Comparison between the ChE activity of various tissues of patient A. N., and the average activity of four subjects who had received no exposure to any anticholinesterase agent and who were autopsied a similar length of time after death due to other causes. The ChE activity is expressed in millimoles of acetylcholine bromide hydrolyzed per minute per gram of tissue per ml. Determinations were made manometrically.<sup>4</sup>

	Cholinesterase Activity		
	Control Average	A. N.	A. N.
	mM ACh Br $\times 10^{-3}$		% of Control Average
Plasma	9.9	0.5	5
Red blood cells	14.0	1.7	12
Liver	3.5	1.5	43
Kidney	2.2	0.9	41
Cerebral cortex	4.8	0.6	12
Thalamus	34.0	12.3	36
Cerebellum	13.1	6.2	47
Pons	7.5	2.4	32
Medulla	3.6	1.2	30

## DETERMINATION OF CHOLINESTERASE ACTIVITY

During the four hours between the time of death and autopsy the body was kept in a refrigerator at 5° C. Determination of the ChE activity of the various tissues was performed four days after the autopsy. During the intervening time the tissues were kept in a refrigerator at 5° C. The ChE activity of the plasma and red blood cells was markedly depressed to 5 and 12 per cent of normal activity. The ChE activity of the liver, kidney and various parts of the brain was also depressed below normal, but, except for the cerebral cortex, the depression was not of the same degree as that of the plasma and red blood cells (table 1). This difference may be due to more rapid restoration of the ChE enzymes of the tissues than of the plasma and red blood cells during the interval between the last exposure to parathion and death. This is suggested by the partial clinical improvement which the patient showed during the three hours prior to death, and by the reported occurrence in experimental animals of delayed death due to parathion, after an initial partial improvement and some restoration of ChE activity of the tissues.<sup>2</sup>

## ANALYSIS FOR PARATHION

Chemical analysis for parathion was performed on the organs removed at autopsy. The procedure used was that of Averell and Norris<sup>10</sup> as modified by Lehman.<sup>11</sup> The modifications involved preliminary drying of the tissues with anhydrous sodium sulfate and subsequent extraction with ether in a Soxhlet extraction apparatus. The ether was evaporated by a stream of air at room temperature and the residue taken up with ethyl alcohol and water and reduced according to the method of Averell and Norris. Control tissues were analyzed at the same time and correction made for these blank values. The results of these analyses, expressed as micrograms of parathion per 100 grams of tissue, were: liver, 148 micrograms; brain, 139 micrograms; kidney, 169 micrograms.

## DISCUSSION

Studies on the effects of related antiChE esters (DFP and TEPP) in man have shown that the slow rate of restoration of ChE enzymes in the tissues following depression by these esters is an important factor in their production of severe cumulative effects.<sup>4-8</sup> The ChE activity of the plasma, red blood cells, and tissues could be considerably reduced without the appearance of cholinergic symptoms, but a further reduction below the level compatible with normal function resulted in marked symptoms.

Examination of the plasma and red blood cells of patient A. N.'s fellow employees, who had had varying degrees of exposure to parathion, revealed that most of them had some depression of ChE activity.<sup>12</sup> Those with more marked depression of ChE activity also had characteristic cholinergic symptoms, while those with lesser degrees of depression of ChE activity had no symptoms. It is very probable that patient A. N. had had some depression of ChE activity of his blood and tissues prior to his last exposure to parathion. On this day, the increased concentration of parathion in the ataclay, and the increased atmospheric temperature and humidity, apparently resulted in a further absorption of parathion, and a depression of ChE activity of the tissues below the level compatible with life.

Following the occurrence of this death due to exposure to parathion, employees at the chemical company in which the death occurred have received periodic determinations of plasma and red blood cell ChE activity, in order to detect those employees who have absorbed this compound.<sup>12</sup> Employees with reduced ChE activity of the plasma or red blood cells have been removed from all exposure to parathion until the ChE activity returned to normal, over a period of several weeks. It is strongly urged that this procedure, as well as all possible safety measures to reduce the degree of exposure and of absorption, be used in any installation or situation in which there is exposure to an antiChE compound, whether in the production, packaging, handling, or spraying of these compounds, in the harvesting of fruits or vegetables on which they have been sprayed, or in their ingestion on insufficiently weathered fruits or vegetables.

The treatment of the effects of excessive exposure or overdose of antiChE compounds relies chiefly on atropine. This may be administered in very large doses in such a situation, as high as 2 to 3 mg. intramuscularly every hour as long as cholinergic symptoms are present, since the tolerance for atropine is greatly increased by the action of the antiChE compound.<sup>8</sup> It is probable that the patient described above should have received larger amounts of atropine than were administered. Other therapeutic measures include washing the skin and gastric lavage to remove any unabsorbed antiChE compound, parenteral replacement of fluids, and administration of oxygen. If muscular weakness is marked and involves the muscles of respiration, intubation and mechanical aid to respiration may become necessary. The administration of curare results in the cessation of muscular fasciculations, but since an overdose may cause weakness of the muscles of respiration, its use is probably not advisable.

### SUMMARY

A report has been presented of a man who died following repeated exposure to the antiChE insecticide, parathion. Safety measures to reduce exposure and absorption, and periodic determinations of plasma and red blood cell ChE activity, are strongly recommended for all persons exposed to this, or any related, antiChE compound.

### BIBLIOGRAPHY

1. HALLER, H. L.: Chemical aspects of some of the newer insecticides, *Bull. N. Y. Acad. Med.*, 1949, xxv, 374-381.
2. DuBois, K. P., DOULL, J., SALERNO, P. R., and COON, J. M.: Studies on the toxicity and mechanism of action of parathion, *Jr. Pharmacol. and Exper. Therap.*, 1949, lxxxv, 79-91.
3. LEHMAN, A. J.: The major toxic actions of insecticides, *Bull. N. Y. Acad. Med.*, 1949, xxv, 382-396.
4. GROB, D., LILIENTHAL, J. L., JR., HARVEY, A. M., and JONES, B. F.: The administration of di-isopropyl fluorophosphate (DFP) to man. I. Effect on plasma and erythrocyte cholinesterase; general systemic effects, use in study of hepatic function and erythropoiesis; and some properties of plasma cholinesterase, *Bull. Johns Hopkins Hosp.*, 1947, lxxxi, 217-244.
5. GROB, D., LILIENTHAL, J. L., JR., and HARVEY, A. M.: The administration of di-isopropyl fluorophosphate (DFP) to man. II. Effect on intestinal motility and use in the treatment of abdominal distention, *Bull. Johns Hopkins Hosp.*, 1947, lxxxi, 245-256.

6. GROB, D., HARVEY, A. M., LANGWORTHY, O. R., and LILIENTHAL, J. L., JR.: The administration of di-isopropyl fluorophosphate (DFP) to man. III. Effect on the central nervous system with special reference to the electrical activity of the brain, *Bull. Johns Hopkins Hosp.*, 1947, lxxxi, 257-266.
7. HARVEY, A. M., LILIENTHAL, J. L., JR., GROB, D., JONES, B. F., and TALBOT, S. A.: The administration of di-isopropyl fluorophosphate (DFP) to man. IV. The effects on neuromuscular function in normal subjects and in myasthenia gravis, *Bull. Johns Hopkins Hosp.*, 1947, lxxxi, 267-292.
8. GROB, D., and HARVEY, A. M.: Observations on the effects of tetraethyl pyrophosphate (TEPP) in man, and on its use in the treatment of myasthenia gravis, *Bull. Johns Hopkins Hosp.*, 1949, lxxxiv, 532-567.
9. MERRILL, G. G.: Neostigmine toxicity. Report of fatality following diagnostic test for myasthenia gravis, *Jr. Am. Med. Assoc.*, 1948, cxxxvii, 362-363.
10. AVERELL, P. R., and NORRIS, M. V.: Estimation of 0,0-diethyl 0, p-nitrophenyl thiophosphate, *Anal. Chem.*, 1948, xx, 753-756.
11. LEHMAN, A. J.: Personal communication.
12. GROB, D., GARLICK, W. L., and HARVEY, A. M.: To be published.

## HEPATOSPLENOMEGALY AND LIVER DAMAGE IN GRAVES' DISEASE\*

By ROBERT S. WALLERSTEIN, Capt., MC, AUS, *Topeka, Kansas* and WELDON J. WALKER, Lt. Col., MC, USA, *Canal Zone, Panama*

LIVER damage as a consequence of thyrotoxicosis is well known. Since the association was first mentioned by Paul<sup>1</sup> in 1865, a considerable literature has developed on the subject. Numerous authors<sup>2-17</sup> have called attention to the occurrence of clinical jaundice as a somewhat rare but by no means unknown concomitant of thyrotoxicosis. In some of these reports<sup>2, 7, 8</sup> the course was that of an acute hepatitis with recovery, in others<sup>3, 12, 13</sup> jaundice did not recede until after successful removal of the inciting toxic thyroid gland, and in others<sup>9, 10, 11, 14, 17</sup> the course was that of an acute yellow atrophy with death. Most writers have agreed that the presence of jaundice is a serious prognostic sign when it occurs in the course of thyrotoxicosis.

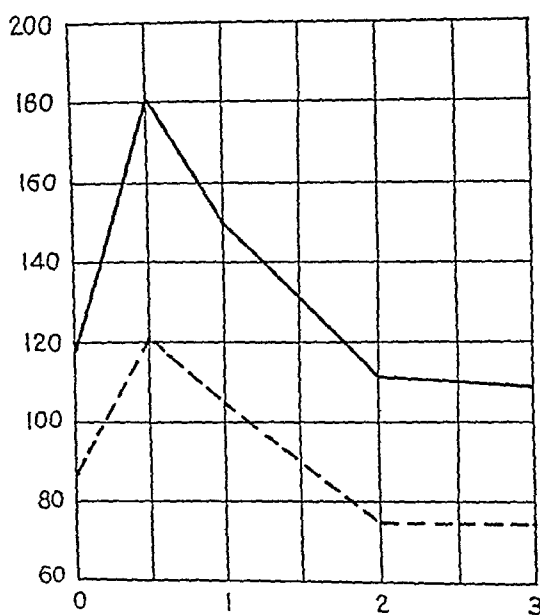
To discover lesser degrees of hepatic damage numerous clinical studies of liver function have been done employing the entire galaxy of available tests. Among these have been such standard liver function tests as the oral and intravenous hippuric acid test,<sup>18-21</sup> galactose tolerance test,<sup>25-29</sup> bromsulfalein retention,<sup>30, 31</sup> prothrombin time,<sup>32</sup> total protein and A/G ratio,<sup>33</sup> blood cholesterol levels,<sup>34</sup> glucose tolerance curves,<sup>35</sup> and the Takata-Ara test.<sup>36</sup> In addition, studies have been made employing the phenoltetrachlorophthalein retention test,<sup>37</sup> the cinchophen oxidation test,<sup>38</sup> and the estimation of the blood amylase level<sup>39</sup> as indicators of liver function. The newest of the liver function tests, the excretion of benzoyl glucuronate,<sup>40</sup> has already been employed in the evaluation of hepatic function in thyrotoxicosis. All of these studies have uniformly demon-

\* Received for publication December 26, 1947.

From the Medical Service, Madigan General Hospital, Tacoma, Washington. Col. Maxwell G. Keeler, MC, Commanding Officer. Col. Albert H. Robinson, MC, Chief of Medical Service.

strated varying incidence of hepatic dysfunction in patients with Graves' disease. In those tests involving the metabolism of carbohydrates (glucose and galactose tolerance tests)<sup>25, 26, 28</sup> the authors pointed out that the abnormal results may be a reflection of multiple derangements of carbohydrate absorption and metabolism in thyrotoxicosis of which impaired hepatic handling is only a part. Therefore these tests may not be a true indication of the severity of hepatic involvement per se.

In addition to these clinical studies there have been parallel investigations of autopsy material in large series of patients who died with Graves' disease, excluding those with known independent hepatic disease.<sup>5, 15, 17, 20, 41-48</sup> With but one exception,<sup>43</sup> these authors have all described a variety of acute and chronic changes, occurring with remarkable consistency, over and beyond the changes of chronic passive congestion secondary to thyrotoxic heart disease. According to



GRAPH 1. Glucose tolerance tests (100 gm. glucose).

Beaver and Pemberton<sup>5</sup> the more acute lesions (fatty changes, central and focal necrosis) have been directly proportional to the severity of the thyrotoxicosis as measured by the basal metabolic rate while the more chronic lesions (atrophy and cirrhosis) have been more related to the duration of the disease.

Duplicating all these clinical studies have been a great many experimental studies in a wide variety of animals, largely rats and dogs but also cats, rabbits, guinea pigs and dormice. Experimental hyperthyroidism has been induced by the feeding of desiccated thyroid gland. The results have been in line with the findings in clinical cases of thyrotoxicosis. Pathological evidence of liver damage was demonstrated<sup>29, 49, 50</sup>; function studies with the use of bromsulfalein retention<sup>51, 52</sup> and IV galactose tolerance tests<sup>29</sup> have shown impairment; marked glycogen depletion of the liver and impaired glycogenesis have been demonstrated<sup>53-56</sup>; and both relative and absolute hypertrophy of the liver and spleen

found after thyroid feeding.<sup>57-60</sup> The depletion of liver glycogen in the thyroid fed mouse was once proposed as a biological test for Graves' disease by Himmelberger<sup>61</sup> who found that blood or urine of thyrotoxic patients injected into mice caused a prompt depletion of liver glycogen. A few authors<sup>62, 63</sup> reported failure to find demonstrable liver damage in experimental animals after thyroid feeding.

Thus there is an impressive body of evidence from functional study, clinical, pathological and experimental sources to establish the presence of impaired hepatic function as an integral part of the syndrome of thyrotoxicosis. Some authors have even drawn a parallel between so-called acute liver death and death in thyroid storm, and, on the basis of similarity in the clinical picture, sought to indict acute liver failure as the major causative factor in death by storm.<sup>20, 61-68</sup>

There is far less agreement, however, about *liver size* in Graves' disease. Experimental work in dogs and rats has indicated that a relative and even absolute hypertrophy of the liver occurs as the animal is made thyrotoxic and caused to lose weight.<sup>57-60</sup> On the other hand most human autopsy studies have shown a reduction in average weight, and simple atrophy has been a common anatomical finding.<sup>5, 15, 17, 44, 69</sup> However, several reports of clinical cases<sup>6, 13, 14</sup> definitely mention various degrees of hepatic enlargement, though most are silent on this point. Perhaps an explanation of the above findings can be effected by recalling the various anatomic changes in the liver seen at post mortem. Acute changes, especially those of fatty infiltration, can certainly cause enlargement of the liver and this would most likely be seen in the clinical cases; whereas the more chronic changes of atrophy and cirrhosis would lead to eventual shrinkage and this would be best seen in autopsy material.

Still less mention has been made of spleen size in the literature. The size of the spleen would be expected to increase with progressive liver involvement and probably continue to increase even when the cirrhotic liver decreases in weight. In two of the reports of experimental work with rats<sup>57, 59</sup> splenomegaly is mentioned; in three autopsy series of patients with Graves' disease the average size of the spleen was found to be normal in one,<sup>69</sup> slightly increased in another,<sup>5</sup> and definitely increased in the third.<sup>44</sup> Two case reports mention splenomegaly as part of the picture of acute hepatic dysfunction in thyrotoxicosis<sup>13, 14</sup> and Means<sup>13</sup> states in his textbook that "The spleen can be palpated in a few cases of toxic goiter."

Therefore, although liver damage in Graves' disease is well known and liver function studies have been incorporated into the preoperative work-up of thyrotoxic patients and been utilized as additional guides to management and to preparation for surgery, the fact that this liver damage can extend to palpable hepatosplenomegaly is far less known. It is thus felt to be of interest to report the following case of thyrotoxicosis with impaired hepatic function and with concomitant hepatosplenomegaly. This case is also of interest because it demonstrates again the reversibility of liver damage on this etiologic basis by proper therapy of the underlying thyrotoxicosis. This reversal of the liver damage is not to be universally expected as some of these patients go on to a progressive and permanent cirrhosis.<sup>6, 23</sup> But certainly the prognosis is much poorer if the relationship of the thyroid as the causative agent is not recognized and the thyrotoxicosis not adequately treated.

## CASE REPORT

A 19 year-old male, in previous excellent health, was admitted on October 3, 1946 with a six to nine month history of nervousness, tremors, weakness, increased appetite, increased sweating, shortness of breath on exertion, evening ankle edema, and slight enlargement of the size of his neck. Initial physical examination revealed: a bilaterally palpable, slightly enlarged thyroid gland, without nodules; a warm moist skin, a slight stare, blood pressure of 145 mm. Hg systolic and 60 mm. diastolic, pulse rate of 108, an apical systolic murmur, a coarse tremor of the extended hands, and palpable liver and spleen each extending about two fingers' breadth below the costal margin. Impression on admission was thyrotoxicosis with hepatosplenomegaly, possibly due to liver damage secondary to Graves' disease.

Initial work-up included the following: basal metabolic rate (average of six calculations) +41; blood cholesterol (average of two) 119 mg. per cent; circulation time (average of two) 8.5 sec.; \* normal blood counts except for a marked lympho-

TABLE I  
Comparison of Tests of Thyroid and Hepatic Function

	On Admission	3 Mos. Postop.
1. Pulse pressure	85	40
2. Pulse rate	108	88
3. Circ. time (calcium gluconate)*	8.5 sec.	15 sec.
4. BMR*	+41	+3
5. Bl cholesterol	119	247
6. Lymphocyte percentage* in blood	67%	47%
7. Liver size	2 F B ↘	2 F B ↘
8. Spleen size	2 F B ↘	barely palpable
9. BSP retention* (5 mg./kilo)	35%	7.5%
10. Oral hippuric test	1.39 G	2.9 G
11. Glucose tolerance curve (see graph)	abnormal	normal
12. Icterus index	7	9
13. Urine for bile and increased urobilinogen	negative	negative
14. Total protein	6.8	7.6
Albumin	5.3	4.4
Globulin	1.5	3.2
15. Prothrombin index	normal	normal

\* Figures refer to average of several determinations.

cytosis of the peripheral blood of (average of three) 66 per cent. It was felt that the above findings of elevated basal metabolic rate, lowered blood cholesterol, decreased circulation time, and lymphocytosis of peripheral blood all fitted with and confirmed the clinical impression of thyrotoxicosis. Electrocardiogram was normal and chest roentgen-ray was normal with no evidence of substernal thyroid.

Because of the hepatosplenomegaly, the hepatic function was investigated. Bromsulfalein retention at 30 min. with 5 mg./kilo was 35 per cent; oral hippuric test revealed excretion of 1.39 gm. benzoic acid; glucose tolerance curve showed 118 mg. per cent fasting level; 180 at one-half hr.; 150 at one hour; 112 at two hours; 109 at three hours. Icterus index 7; total protein 6.8 gm. per cent with 5.3 gm. albumin and 1.5 gm. globulin. The urine was negative for bile and for increased urobilinogen; prothrombin index normal. Though some of these tests were normal, the more sensitive ones, bromsulfalein and oral hippuric, revealed a considerable degree of hepatic

\* 3 c.c. calcium gluconate intravenously: arm to tongue time.



dysfunction and the glucose tolerance test showed a slight derangement of carbohydrate metabolism.

In an effort to rule out other possible causes of hepatosplenomegaly the following additional determinations were made: fragility of red cells, normal; malarial smears after adrenalin, negative; bleeding time two minutes, clotting time 1 min. 35 sec., reticulocyte count .1 per cent, platelet count 158,400. Hematocrit was 45 per cent, sedimentation rate 9 mm./hr. (Wintrobe method), urinalysis normal, Kahn negative.

After completion of these studies patient was prepared for surgery with Lugolization, high caloric diet, rest, sedation, and B vitamin supplements. The basal metabolic rate gradually fell to +27 and after three weeks it was decided to operate. Immediately preoperatively bromsulfalein retention had fallen to 25 per cent in 30 min., and the oral hippuric test showed a rise in benzoic acid excretion to 2.55 gm.

Subtotal, one stage thyroidectomy was performed on December 17, 1946 under endotracheal gas-oxygen-ether anesthesia. Patient stood the procedure well and convalesced uneventfully. Pathological report on the excised thyroid gland revealed "small acini, lined by columnar epithelium, having no colloid. Some acini showed papillary infoldings and some larger acini contained eosin staining colloid. Definite increase in lymphocytic elements of the stroma and in some areas definite lymph follicles were noted. Diagnosis: Diffuse hyperplasia of thyroid with areas of regression."

Post-operatively basal metabolic rate determinations were +1. and +1. Bromsulfalein retention was 20 per cent at 30 minutes, oral hippuric test showed 2.08 gm. excretion, icterus index was 7, urine showed no bile and was positive for urobilinogen in 1:20 dilution. The liver and spleen were palpable as before. It was felt that the immediate postoperative period was too early to evaluate the possible effect of thyroidectomy on restoration of liver function and regression of liver and spleen size.

Patient was accordingly sent on a 60 day convalescent furlough and returned for reevaluation on March 13, 1947. During the interval, patient had been in excellent health. Upon his return his blood pressure was 130 mm. Hg systolic and 90 mm. diastolic, his pulse 88, his spleen definitely smaller in size and now barely palpable, his liver apparently unchanged in size. Thyroid and liver function were both reevaluated.

Basal metabolic rate was +6, and 0; blood cholesterol 247; circulation time 15 sec., 15 sec.; white blood count 9,800 with 51 per cent polys and 47 per cent lymphocytes. The electrocardiogram and chest roentgen-ray were again normal as was hematocrit, white count, platelet count, sedimentation rate, urinalysis. Liver function studies revealed the following. Bromsulfalein (5 mg./kilo at 30 min.), 10 per cent and 5 per cent retention; oral hippuric excretion test 2.9 gm. benzoic acid; thymol turbidity 6 units (normal 0 to 10); cephalic flocculation 1+ (unfortunately it had not been possible to obtain the last two mentioned tests preoperatively); glucose tolerance curve, 88 fasting level, 121 at one-half hour, 104 at one hour, 75 at two hours and 75 at three hours; total protein 7.6 gm. per cent with albumin 4.4 and globulin 3.2 gm.; prothrombin index normal, icterus index 9, urine negative for bile and for increased urobilinogen.

Thus three months postoperatively, not only had all clinical and chemical evidences of thyrotoxicosis reverted to normal but the spleen had definitely decreased in size and the results of all liver function tests revealed no significant abnormality.

#### COMMENT

Because of the rarity of reported hepatosplenomegaly as concomitants of thyrotoxicosis, numerous other diagnostic possibilities were explored in the work-up of this patient. The combination of hepatomegaly, splenomegaly and the marked lymphocytosis of the peripheral blood (64, 61, and 75 per cent) suggested the possibility of a somewhat atypical lymphatic leukemia with the associ-

ated elevated basal metabolic rate so often seen in leukemic patients. The absence of lymphadenopathy, of immature white cells in the peripheral blood and of anemia served to exclude this possibility. The reversal of the peripheral blood picture and of the splenomegaly after thyroidectomy was further evidence against the diagnosis of leukemia. The absence of increased red cell fragility, of spherocytes on blood smear, of signs of increased hemolysis, and of reticulocytosis served readily to differentiate familial hemolytic icterus. The patient had never been in a malarious area, had no history of fever and chills, and repeated smears after adrenalin were negative for malaria.

That the liver damage and hepatomegaly were not part of an independent cirrhosis of the liver was established by the reversal of the picture subsequent to thyroidectomy. There was incidentally no history of alcoholism or dietary deficiency of any type. The absence of icterus, of gastrointestinal symptoms, especially anorexia and nausea, and of the signs of acute illness ruled out a concomitant but unrelated acute infectious hepatitis. We were therefore left with the conclusion, amply supported by the evidence cited from the literature, that we were dealing with a case of liver damage secondary to thyrotoxicosis and that in this case the liver damage extended to the admittedly more rare presence of definite hepatosplenomegaly. This case is being reported largely to call attention to the fact that hepatosplenomegaly occurring in conjunction with Graves' disease can be part of the clinical picture and that it together with the chemical evidences of hepatic dysfunction can be expected to reverse itself when the underlying thyrotoxicosis is adequately treated.

The obvious corollary is that a careful evaluation of the hepatic function should be part of the work-up of every thyrotoxic patient, especially those in whom surgery is contemplated. The importance of this preoperative evaluation and the preoperative fortification of the damaged liver is stressed by numerous writers on this subject.<sup>20, 21, 24, 66, 68, 70, 71</sup> Of 250 patients with thyrotoxicosis seen in Schmidt's clinic, 60 per cent had a definite impairment of liver function on the basis of the oral hippuric acid test.<sup>24</sup> The magnitude of this relationship needs constant reëmphasis.

### SUMMARY

A case of relatively mild thyrotoxicosis with marked liver damage and secondary hepatosplenomegaly is presented. Attention is called to the fact that the liver damage so often found in patients with Graves' disease can be severe enough to cause definite enlargement of the liver and spleen and that these findings though unusual are not incompatible with the clinical picture of thyrotoxicosis. The hepatic dysfunction was reversed by subtotal thyroidectomy.

### BIBLIOGRAPHY

1. PAUL, quoted by SHAFFER, J. M.<sup>15</sup>
2. ACREE, F. M.: Graves' disease complicated by acute catarrhal jaundice; case report, *Trans. Am. Assoc. Goiter*, 1939, 50-52.
3. BARB, J. S., and LOURIA, H. W.: Jaundice associated with toxic goiter, *Am. Jr. Surg.*, 1936, xxxiv, 338.
4. BARKER, L. F.: Thyreo-intoxication with necrosis and atrophy of the liver, damage to the heart muscle and kidneys and terminal broncho-pneumonia, *Med. Clin. N. Am.*, 1930, xiv, 261-263.

5. BEAVER, D. C., and PEMBERTON, J. DE J.: The pathologic anatomy of the liver in exophthalmic goiter, *Ann. Int. Med.*, 1933, vii, 687-708.
6. BERK, J. E., and GOLDBURGH, H. L.: The etiology and significance of hepatic changes in hyperthyroidism, *Internat. Clin.*, 1941, iv, 126-134.
7. BURTON, F. W.: Pigmentation and other cutaneous affections in Graves' disease, *Lancet*, 1888, ii, 573-574.
8. EDER, M. D.: Three cases of jaundice occurring in persons suffering from exophthalmic goiter, *Lancet*, 1906, i, 1758.
9. HABERSHON: Exophthalmic goiter, heart disease; jaundice; death, *Lancet*, 1874, i, 510.
10. KERR, W. J.: Necrosis of heart and liver in thyrotoxicosis with some notes on possible changes in other organs, *Northwest Med.*, 1930, xxix, 430-431.
11. KERR, W. J., and RUSK, G. Y.: Acute yellow atrophy associated with hyperthyroidism, *Med. Clin. N. Am.*, 1922, vi, 445-459.
12. MAHORNER, H. R.: Jaundice associated with hyperthyroidism, *New Orleans Med. and Surg. Jr.*, 1934, lxxxvii, 382-386.
13. MEANS, J. H.: The thyroid and its diseases, 1937.
14. REZEK, P. R.: Relation between Graves' disease and liver pathology: importance in the use of thiouracil, *South. Med. Jr.*, 1947, x1, 166-171.
15. SHAFFER, J. M.: Disease of the liver in hyperthyroidism, *Arch. Path.*, 1940, xxix, 20-30.
16. SUTCLIFF, E. H.: An extraordinarily acute case of Graves' disease, *Lancet*, 1898, i, 717.
17. WYNDHAM, N.: Liver damage in thyrotoxicosis, *Australian and N. Zealand Jr. Surg.*, 1939-40, ix, 385-392.
18. BARTELS, E. C.: Liver function in hyperthyroidism as determined by the hippuric acid test, *Ann. Int. Med.*, 1938, xii, 652-674.
19. BARTELS, E. C., and PERKINS, H. J.: Liver function in hyperthyroidism as determined by the hippuric acid test, *New Eng. Jr. Med.*, 1937, ccxvi, 1051-1060.
20. BOYCE, F. F.: The rôle of the liver in surgery, 1941, Charles C. Thomas Co., Springfield, Illinois.
21. BOYCE, F. F., and McFETRIDGE, E. M.: Studies of hepatic function by the Quick hippuric acid test. II. Thyroid disease, *Arch. Surg.*, 1938, xxxvii, 427-442.
22. HAINES, S. F., MAGATH, T. B., and POWER, M. H.: The hippuric acid test in hyperthyroidism, *Ann. Int. Med.*, 1941, xiv, 1225-1231.
23. MILLS, F. H.: An investigation of hepatic function in thyrotoxicosis, *Med. Jr. Australia*, 1942, i, 195-198 (correction p. 274).
24. SCHMIDT, C. R.: Hepatic insufficiency in toxic goiter and its treatment. In HERTZLER, A. E.: Diseases of the thyroid gland, 1941, New York, 529-548.
25. ALTHAUSEN, T. L., LOCKART, J. C., and SOLEY, M. H.: A new diagnostic test (galactose) for thyroid disease, *Am. Jr. Med. Sci.*, 1940, cxcix, 343-351.
26. ALTHAUSEN, T. L., and WEVER, G. K.: Galactose tolerance in hyperthyroidism, *Jr. Clin. Invest.*, 1937, xvi, 257-259.
27. LICHTMAN, S. S.: Liver function in hyperthyroidism with special reference to the galactose tolerance test, *Ann. Int. Med.*, 1940-41, xiv, 1199-1215.
28. MACLAGEN, N. F.: Galactose tolerance in jaundice and hyperthyroidism, *Proc. Roy. Soc. Med.*, 1941, xxxiv, 602-606.
29. MACLAGEN, N. F., and RUNDLE, F. F., with experimental data by COLLARD, H. B., MILLS, F. H., and RUNDLE, F. F.: Liver function in thyrotoxicosis, *Quart. Jr. Med.*, 1940, ix, 215-228.
30. MADDOCK, W. G., COLLIER, F. A., and PEDERSEN, S.: Thyroid crisis: its relation to liver function and adrenalin, *West. Jr. Surg.*, 1936, xlv, 513-521.
31. MADDOCK, W. G., PEDERSEN, S., and COLLIER, F. A.: Studies of the blood chemistry in thyroid crisis, *Jr. Am. Med. Assoc.*, 1937, cix, 2130-2135.
32. LORD, J. W., JR., and ANDRUS, W. DE W.: Changes in liver associated with hyperthyroidism, *Arch. Surg.*, 1941, xlii, 643-660.

33. BARTELS, E. C.: Serum protein studies in hyperthyroidism, *New Eng. Jr. Med.*, 1938, ccxviii, 289-294.
34. HURXTHAL, L. M.: Blood cholesterol in thyroid disease. II. Effect of treatment, *Arch. Int. Med.*, 1933, lii, 86-95.
35. SANGER, B. J., and HUN, E. G.: Glucose mobilization rate in hyperthyroidism, *Arch. Int. Med.*, 1922, xxx, 397-406.
36. RAGINS, A. B.: The value of the Takata and Ara reaction as a diagnostic and prognostic aid in cirrhosis of the liver, *Jr. Lab. and Clin. Med.*, 1935, xx, 902-913.
37. YOUNG, J. B., and WARFIELD, L. M.: Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency, *Arch. Int. Med.*, 1926, xxxvii, 1-17.
38. LICHTMAN, S. S.: Liver function in hyperthyroidism, *Arch. Int. Med.*, 1932, i, 721-729.
39. BARTLETT, W., JR.: Role of the liver in thyrotoxicosis, *Surgery*, 1938, iii, 261-262.
40. SNAPPER, I., and SALTZMAN, A.: Excretion of benzoyl glucuronate as a test of liver function, *Am. Jr. Med.*, 1947, ii, 334-341.
41. CAMERON, G. R., and KARUNARATNE, W. A. E.: Liver changes in exophthalmic goiter, *Jr. Path. and Bact.*, 1935, xli, 267-282.
42. HABÁN, G.: Über die Leberveränderungen bei Morbes Basedowii mit besonderer Berücksichtigung der Lebercirrhose, *Beitr. path. Anat.*, 1933-34, xcii, 88-100.
43. LEWIS, W.: Hyperthyroidism and associated pathology, *Am. Jr. Med. Sci.*, 1931, clxxxix, 65-74.
44. MARINE, D., and LENHART, C. H.: Pathological anatomy of exophthalmic goiter, *Arch. Int. Med.*, 1911, viii, 265-316.
45. MOSCHOWITZ, E.: Pathogenesis of cirrhosis of the liver occurring in patients with diffuse toxic goiter, *Arch. Int. Med.*, 1946, lxxviii, 497-530.
46. RÖSSLE, R.: Über die Veränderungen der Leber bei der Basedowschen Krankheit und ihre Bedeutung für die Entstehung anderer Organsklerosen, *Virchow's Arch.*, 1933, ccxc, 1-46.
47. WELLER, C. V.: Hepatic lesions associated with exophthalmic goiter, *Trans. Assoc. Am. Phys.*, 1930, xlv, 71-76.
48. WELLER, C. V.: Hepatic pathology in exophthalmic goiter, *Ann. Int. Med.*, 1933, vii, 543-560.
49. FARRANT, R.: Hyperthyroidism, its experimental production in animals, *Brit. Med. Jr.*, 1913, ii, 1363-1367.
50. HASHIMOTO, H.: The heart in experimental hyperthyroidism with special reference to its histology, *Endocrinology*, 1921, v, 579-606.
51. DRILL, V. A., and HAYS, H. W.: Studies on the relation of the liver function, pulse rate, and temperature of hyperthyroid dogs to vitamin B<sub>1</sub> and yeast, *Am. Jr. Physiol.*, 1942, cxxxvi, 762-771.
52. DRILL, V. A., SHAFFER, C. B., and OVERMAN, RICHARD: Liver function, pulse rate and temperature of hyperthyroid dogs. Effects of a yeast-free diet and a high B vitamin diet, *Am. Jr. Physiol.*, 1943, cxxxviii, 370-377.
53. BUELL, M. V., and STRAUSS, M. B.: Liver function in experimental hyperthyroidism, *Jr. Biol. Chem.*, 1934, xiv, 105.
54. COGGESHALL, H. C., and GREENE, J. A.: The influence of desiccated thyroid gland, thyroxin, and inorganic iodine, upon the storage of glycogen in the liver of the albino rat under controlled conditions, *Am. Jr. Physiol.*, 1933, cv, 103-109.
55. DRILL, V. A.: The effect of yeast on the liver glycogen of white rats during hyperthyroidism, *Jr. Nutr.*, 1937, xiv, 355-363.
56. FRAZIER, C. H., and FRIEMAN, H.: Alterations in liver glycogen following thyroid, iodine, and glucose feedings, *Surg., Gynec. and Obst.*, 1935, lx, 27-29.
57. HEWITT, J. A.: The effect of administration of small amounts of thyroid gland on the size and weight of certain organs in the male white rat, *Quart. Jr. Exper. Physiol.*, 1919-20, xii, 347-354.

58. HIGGINS, G. M.: Experimental pathology of the liver. XII. Effects of feeding desiccated thyroid gland on restoration of the liver, *Arch. Path.*, 1933, xvi, 226-231.
59. HOSKINS, E. R.: The growth of the body and organs of the albino rat as affected by feeding various ductless glands (thyroid, thymus, hypophysis, and pineal), *Jr. Exper. Zool.*, 1916, xx, 295-346.
60. SIMONDS, J. P., and BRANDES, W. W.: The effect of experimental hyperthyroidism and of inanition on the heart, liver, and kidney, *Arch. Path.*, 1930, ix, 445-460.
61. HIMMELBERGER, L. R.: A thyroid hormone in the blood and urine in Graves' disease, preliminary report, *Endocrinology*, 1932, xvi, 264-266.
62. DRILL, V. A., and GUNN, F. D.: Hepatic lesions and experimental hyperthyroidism, *Endocrinology*, 1944, xxxv, 477-482.
63. SEALY, W. C.: Rôle of infection in the pathogenesis of liver necrosis in hyperthyroidism, *Ann. Surg.*, 1942, cxvi, 851-859.
64. BOYCE, F. F., and McFETRIDGE, E. M.: The rôle of liver damage in the mortality of surgical disease, *South. Med. Jr.*, 1938, xxxi, 35-39.
65. DINSMORE, R. S.: Factors influencing morbidity in thyroid surgery, *Jr. Am. Med. Assoc.*, 1937, cix, 179-183.
66. FICARRA, B. J., and NACLERIO, E. A.: Thyroid crisis: pathogenesis of hepatic origin, *Am. Jr. Surg.*, 1945, lxxix, 325-337.
67. FOSS, H. L., HUNT, H. F., and McMILLAN, R. M.: The pathogenesis of crisis and death in hyperthyroidism, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1090-1094.
68. LAHEY, F. H.: The reduction of the mortality in hyperthyroidism, *New Eng. Jr. Med.*, 1935, ccxiii, 475-479.
69. AHRONHEIM, J. H.: The size of the spleen and the liver-spleen ratio. A statistical study based on one thousand autopsies, *Arch. Path.*, 1937, xxiii, 33-52.
70. FRAZIER, C. H., and BROWN, R. B.: The thyroid and the liver, *Trans. Am. Assoc. Study of Goiter*, 1935, 168-178.
71. FRAZIER, C. H., and BROWN, R. B.: The thyroid and the liver, *West Jr. Surg., Obst. and Gynec.*, 1935, xliii, 636-646.

---

## GREAT REDUCTION IN HEART SIZE ATTENDING THE CLEARING OF CONGESTIVE HEART FAILURE IN A MAN WITH HYPERTENSIVE AND CORONARY HEART DISEASE\*

By JAMES H. CURRENS, M.D., and PAUL D. WHITE, M.D., F.A.C.P.,  
*Boston, Massachusetts*

THE treatment of many patients with cardiac dropsy has been discouraging in the past in spite of the use of digitalis and mercurial diuretics which oftentimes give striking temporary improvement. In the majority of patients with congestive failure resulting from hypertensive and coronary heart disease, however, experience has shown that edema and dyspnea return with monotonous regularity even though activities are kept at a minimum. In the past few years the importance of a low sodium dietary intake has become increasingly apparent as a means of preventing the re-appearance of all the signs of congestive heart failure, particularly among the patients with coronary and/or hypertensive heart disease.

We wish to present the following case report demonstrating what may be accomplished in certain patients who on initial examination show severe cardiac dropsy. This report demonstrates the reversibility of symptomatic heart disease

\* Received for publication August 28, 1947.

in a patient with hypertensive and coronary heart disease by the use of all the measures which are available to the physician of today.

#### CASE REPORT

A 61 year old physician was first seen in August, 1945, because of shortness of breath and dependent edema. The patient had always enjoyed good health, although he had been somewhat nervous all of his life. Seven years previously his blood pressure had been found to be elevated, the systolic level ranging from 180 to 200 millimeters of mercury. One year previously, in July, 1944, the patient was taken in the street with severe left anterior chest pain with radiation to the left arm. The pain lasted for 45 minutes, being relieved at that time by morphine. The following day, while he was at home in bed, the pain recurred and lasted one hour, again requiring morphine for relief. The patient was seen at this time by a competent cardiologist, and after reviewing the electrocardiograms he felt that the patient was suffering from coronary insufficiency but did not believe that a myocardial infarction had occurred. The patient was in bed four weeks and about the house for another month, after which time he returned to work.



FIG. 1.

A. Teleroentgenogram of the chest on July 25, 1945, demonstrating a large heart measuring 19.6 centimeters in diameter.

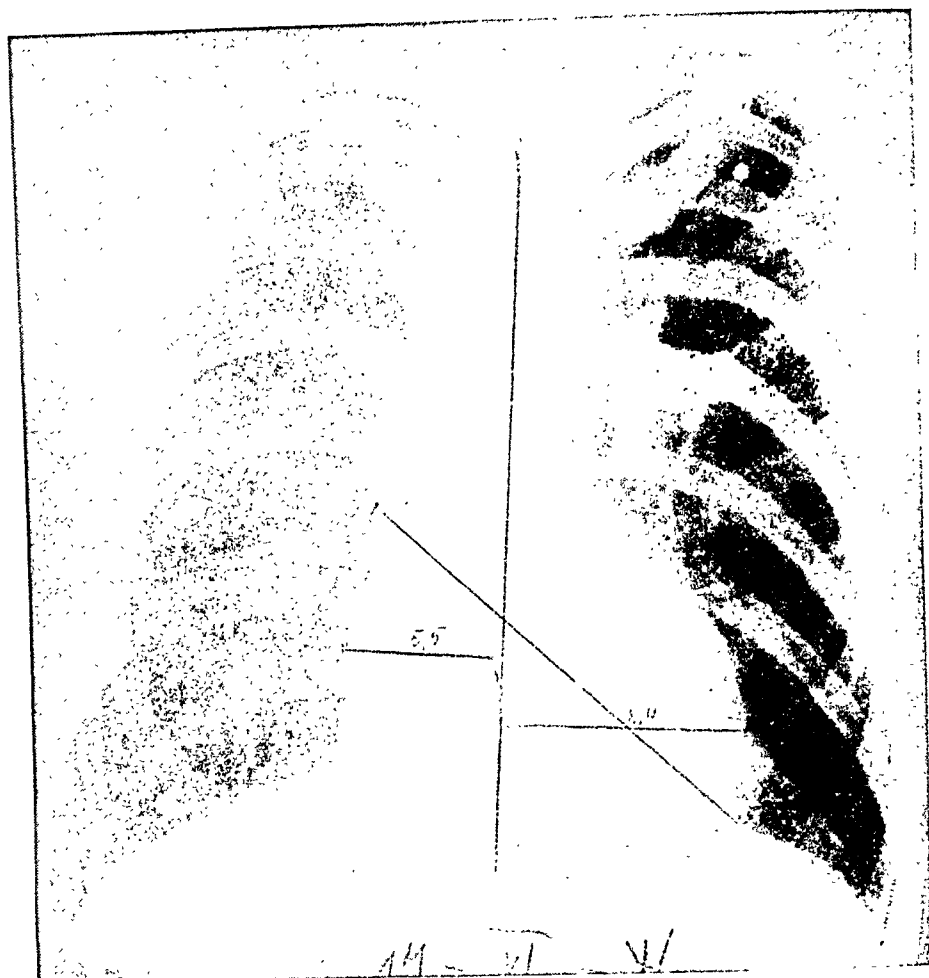


FIG. 1.

B. Repeat teleroentgenogram on June 12, 1946, shows a remarkable decrease in the size of the heart to 13.9 centimeters. The heart was found to be this same size in April, 1947.

Six months later, in February, 1946, the patient had an attack of paroxysmal nocturnal dyspnea, at which time he was placed upon digitalis and aminophyllin. He remained in bed at that time for one week. The following month he developed considerable dyspnea on effort and dependent edema in spite of his medication. His condition became gradually worse in spite of ammonium chloride and infrequent mercurial diuresis.

On physical examination the patient was found to have considerable orthopnea. The neck veins were distended and pulsating. A moderate number of moist râles were heard at each lung base. The heart was found to be considerably enlarged and the sounds were of poor quality. There was a loud apical protodiastolic gallop rhythm and the pulmonary second sound was accentuated. The blood pressure was 180 millimeters of mercury systolic and 116 millimeters diastolic, with a pulsus alternans of 2 to 4 millimeters of mercury. The liver was three to four fingers'-breadth below the right costal margin, and there was a high degree of edema of the sacrum and lower extremities. A chest film taken a few weeks before is illustrated in figure 1; the electrocardiograms at that time and subsequently are illustrated in figure 2.

The patient's revised treatment consisted of increasing the dosage of ammonium chloride from 3 grams to 6 grams per day and of digitalis to 0.2 gram each day for 10 days and mercurial diuresis (2 c.c. of Mercupurin) on three occasions. He was also placed upon a low sodium dietary regime. The diet contained about 0.5 gram of sodium per day with a neutral ash content. The fluids were increased from about 1400 c.c. a day to around 2000 c.c. a day. In the course of the next few weeks

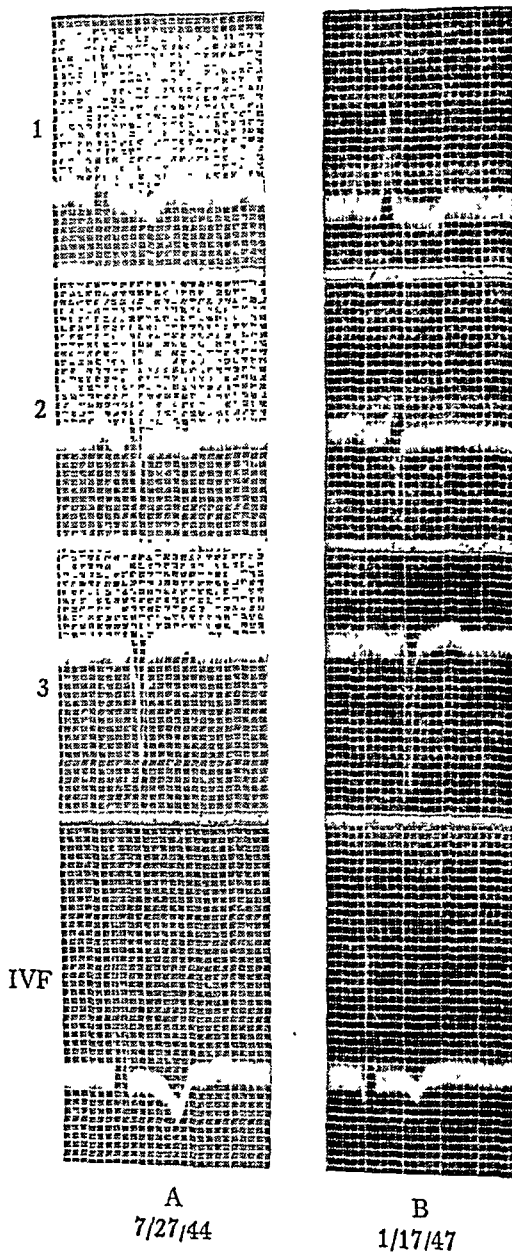


FIG. 2.

A. The electrocardiogram taken in July, 1944, several days after the patient had severe chest pain on two successive days. The pattern is quite characteristic of left ventricular strain and hypertrophy with or without the presence of coronary heart disease.

B. Repeat electrocardiogram of January, 1947, reveals little change, although the T waves in Leads I and IV are somewhat less negative and the R waves in Leads I and II shorter. There has been surprisingly little variation in the tracings from July, 1944, to January, 1947.



the patient lost 30 pounds in weight, the anasarca subsided, and the patient subjectively felt much improved.

The patient was last seen by us in April, 1947, almost two years after the first examination, at which time he was feeling well indeed, and he had had no recurrence of dyspnea or edema. He has continued with 0.1 gram of digitalis and 3 grams of ammonium chloride each day, and he has been very careful to avoid foods which contain any appreciable amounts of sodium. His food is cooked without salt, including his bread, but otherwise he eats a well-rounded diet. Fluids are taken as needed, which amounts to two to two and one-half liters each day.

Physical examination in April, 1947, revealed no evidence of venous pulsation in the neck, and no râles were heard in the chest. The heart was found to be on the borderline as to cardiac enlargement and the apex impulse was 8 centimeters to the left of the mid-sternal line in the fifth interspace. There were no murmurs or gallop rhythm. The blood pressure was 170 millimeters of mercury systolic and 104 to 110 millimeters diastolic. The liver was not palpable. No edema was discernible in the lower extremities. The blood and urine examinations showed no abnormalities. The non-protein nitrogen measured 25 milligrams per cent. A phenolsulphonephthalein urinary excretion test indicated 47 per cent excretion in two hours with 15 per cent excretion in the first 15 minutes. A roentgen-ray film demonstrated a striking reduction in the size of the cardiac silhouette in comparison with the chest film of July, 1945, and was similar to the film in figure 1B. The transverse diameter of the heart shadow had decreased by 5.7 centimeters.

He continues to do well, spending 12 hours a day in bed and doing not more than two hours of office work each day. A salt substitute containing equal parts of potassium chloride and potassium citrate has been used at times, but generally he does without this substitute. Although the food tastes quite flat, he seems to have adjusted himself well to the diet and does not feel the need for a salt substitute.

## DISCUSSION

The judicious increase in dosage of digitalis and ammonium chloride and in sodium restriction together with the use of mercurial salts parenterally resulted in a striking diuresis in this patient. In a relatively short period of time the dropsy disappeared and he was free of his bothersome orthopnea and dyspnea. During this time the amount of sodium lost in the urine must have been large, for we know that a person may lose 30 to 40 grams of sodium as sodium chloride following mercurial diuresis.

The use of the low-sodium diet was of the utmost importance from the long-range point of view since it helped prevent the re-accumulation of the dropsy. Without such a regimen it has been our experience in the past that the majority of these patients require periodic mercurial diuresis to maintain any reasonable health. By the use of mercurial diuretics one effectually increases the loss of water and sodium chloride. It is, however, more advantageous to limit the intake of sodium in order to prevent the accumulation of the dropsy as has been suggested repeatedly since 1941.<sup>1-5</sup>

The striking decrease in heart size is attributed to the decrease in blood volume time effected by the diuresis aided doubtless by adequate digitalization. The size of the heart has been found to reflect roughly the circulating blood volume. The reduction in size of this patient's heart has been greater than in most patients observed (except for a few myxedematous cases) in whom the reduction had been effected by sympathectomy or dietary treatment for hypertension or by subsidence of congestive heart failure with digitalization.

It is interesting to note that in spite of this remarkable reduction in heart size there was no commensurate improvement of the electrocardiogram, although there was a slight return toward the normal (figure 2). This is possibly accounted for by the presence of coronary heart disease with very likely some scarring of the myocardium. The continued hypertension may also be an important factor in the persistent electrocardiographic pattern. The change in the blood pressure was not remarkable in spite of the low sodium intake over a prolonged period of time. Other diets have been reported to be of value in the treatment of cardiac dropsy, the salient feature of which undoubtedly is the low sodium content.<sup>4, 6, 7</sup> An additional item of some importance in the course of this man's recovery may have been a subsidence of activity of coronary heart disease through the spontaneous development of collateral circulation which is of such common occurrence in the evolution of disease of the coronary arteries.

### SUMMARY

Remarkable decrease in heart size is reported in the case of a man aged 61 years treated for severe congestive heart failure secondary to hypertension and coronary arterial disease. The therapy included adequate digitalization, the use of ammonium chloride and mercurial diuretic, and a sharp restriction of sodium intake. The sodium restriction was in large measure doubtless responsible for the two years of good health that followed.

We wish to acknowledge the coöperation of Dr. Roberto Zachrisson, Guatemala City in the case of this patient.

### BIBLIOGRAPHY

1. SCHROEDER, H. A.: Studies in congestive heart failure, *Am. Heart Jr.*, 1941, xxii, 141.
2. PROGER, S., GINSBURG, E., and MAGENDANTZ, H.: Effects of ingestion of excessive amounts of sodium chloride and water on patients with heart disease, *Am. Heart Jr.*, 1942, xxiii, 555.
3. ELLIS, L. B.: Relative importance of salt and fluid in the management of congestive heart failure, *Trans. New Eng. Heart Assoc.*, 1942, 33-34.
4. SCHEMM, F. R.: High fluid intake in management of edema, especially cardiac edema. I. Details and bases of regime, *Ann. Int. Med.*, 1942, xvii, 952; High fluid intake in management of edema, especially cardiac edema. II. Clinical observations and data, *Ann. Int. Med.*, 1944, xxi, 937.
5. WHEELER, E. O., BRIDGES, W. C., and WHITE, P. D.: Diet low in salt (sodium) in congestive heart failure, *Jr. Am. Med. Assoc.*, 1947, xvi, 133.
6. KEMPNER, WALTER: Treatment of cardiac failure with the rice diet, *North Carolina Med. Jr.*, 1947, viii, 128.
7. KARRELL, P.: De le cure de lait, *Arch. gén. de méd.*, 1866, ii, 513.

## MYOCARDIAL INFARCTION RESULTING IN INTERVENTRICULAR SEPTAL PERFORATION; REPORT OF A CASE DIAGNOSED DURING LIFE \*

By L. J. BICKERMAN, M.D., *Peoria, Illinois*, and ERNEST E. IRONS, M.D.,  
F.A.C.P., *Chicago, Illinois*

THIS report concerns a case of coronary thrombosis with infarction of the interventricular septum, in which perforation of the septum was diagnosed during life. Sager,<sup>1</sup> in 1934, gathered from the literature only 18 recorded cases (including one of his own) of perforation of the infarcted interventricular septum, the first of which was reported by Latham in 1845.<sup>2</sup> Wood and Livezey<sup>4</sup> found reference to 36 cases up to 1942. In a series of 25,000 consecutive autopsies, Edmondson and Hoxie<sup>3</sup> found 72 cases of cardiac rupture, among them 13 cases of septal perforation due to infarction. Additional cases have been reported by Moolton, Lober and Herzog, Wood, Weber, Bayley and Fader, Scott and Garvin, Master and Russell, Gross and Schwartz, and Stanley.

### CASE REPORT

The patient, a woman aged 72 years, was admitted to Presbyterian Hospital, Chicago, on October 3, 1946, complaining of severe substernal pain with radiation down both arms into the forearms.

The patient had been aware of the existence of hypertension for a number of years (1934: blood pressure 160/95; 1940: 190/110; 1942: 155/90). She had been in good health until three days prior to admission, when, while shopping, she suffered severe "knot-like" substernal pain and a severe pain in the right shoulder and back accompanied by faintness and slight nausea. She returned to her hotel where she rested until the following evening, when, feeling quite well, she attended a theater, after which severe substernal pain recurred with radiation into both forearms. The patient was seen that evening by a physician who prescribed a hypodermic injection after which the patient felt better. The following morning she was awakened by a recurrence of pain with the previous radiation, called a doctor, and was hospitalized within a short time.

Physical examination revealed an elderly, moderately obese woman complaining of substernal pain and appearing pale and fatigued. Temperature on admission was 99.2 degrees; pulse rate 88 per minute; respirations 18 per minute; blood pressure 138/90. The pupils were moderately contracted (morphine) but reacted to light. Lungs were clear. Heart tones were noted to be distant, and no murmurs were audible. The rhythm was regular and no enlargement was noted on percussion of the cardiac borders. The liver was not palpable. There was no peripheral edema. Sedimentation rate (corrected) was 49 mm. per hour; white blood count 15,000 per cu. mm. The electrocardiogram was interpreted as indicating left axis deviation, anterior myocardial infarction, probably recent. Septal involvement was suggested on the basis of widening of QRS complexes (figure 1a).

The patient was free of additional symptoms from October 4, 1946, until the evening of October 7, when slight nausea was noted. The blood pressure had fallen to 118/70, the pulse rate had risen to 96 per minute, and the patient continued to show an elevation of temperature between 99.4 and 100.2 degrees. An electrocardiogram

\* Received for publication September 15, 1947.

From the Medical Clinic, Presbyterian Hospital, Chicago, Illinois.

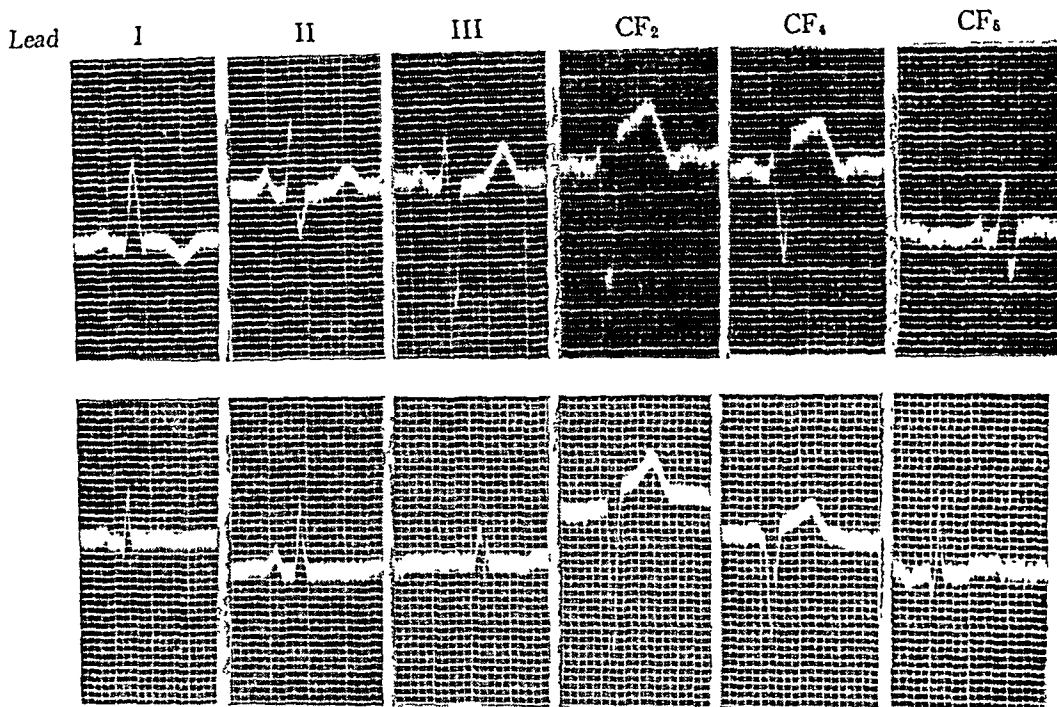


FIG. 1 A. (above) October 4, 1946. Day following admission to hospital.

FIG. 1 B. (below) October 7, 1946. Three days after admission to hospital.

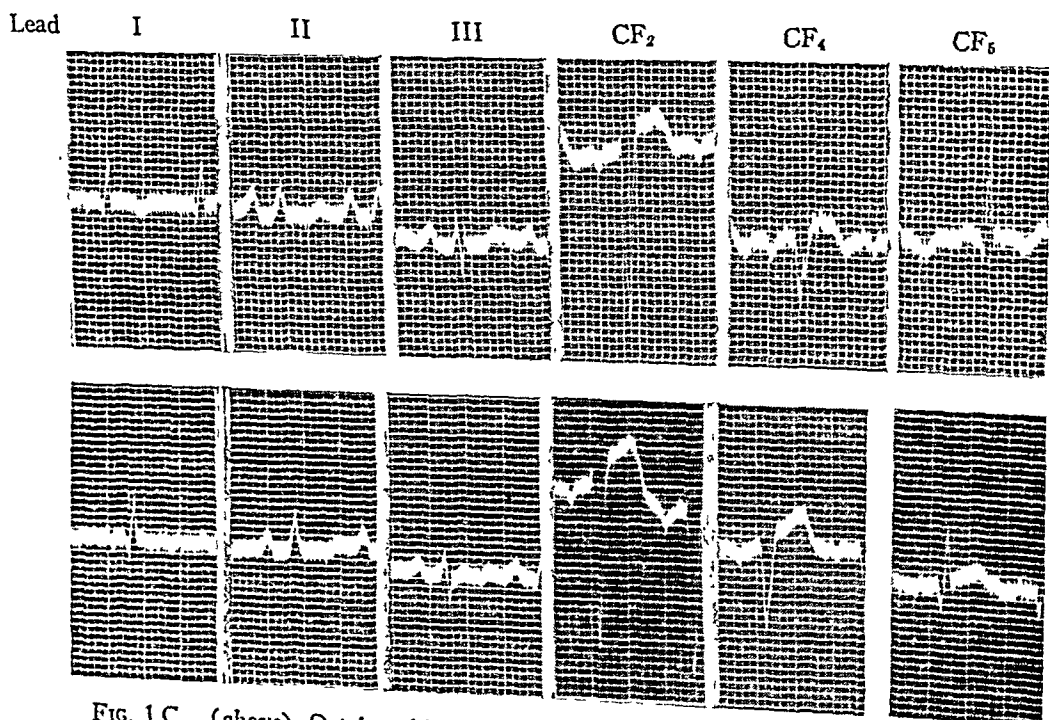


FIG. 1 C. (above) October 14, 1946. Ten days after admission, and six hours after septal perforation.

FIG. 1 D. (below) October 16, 1946. Twelve days after admission; two days after septal perforation, and four days prior to death.

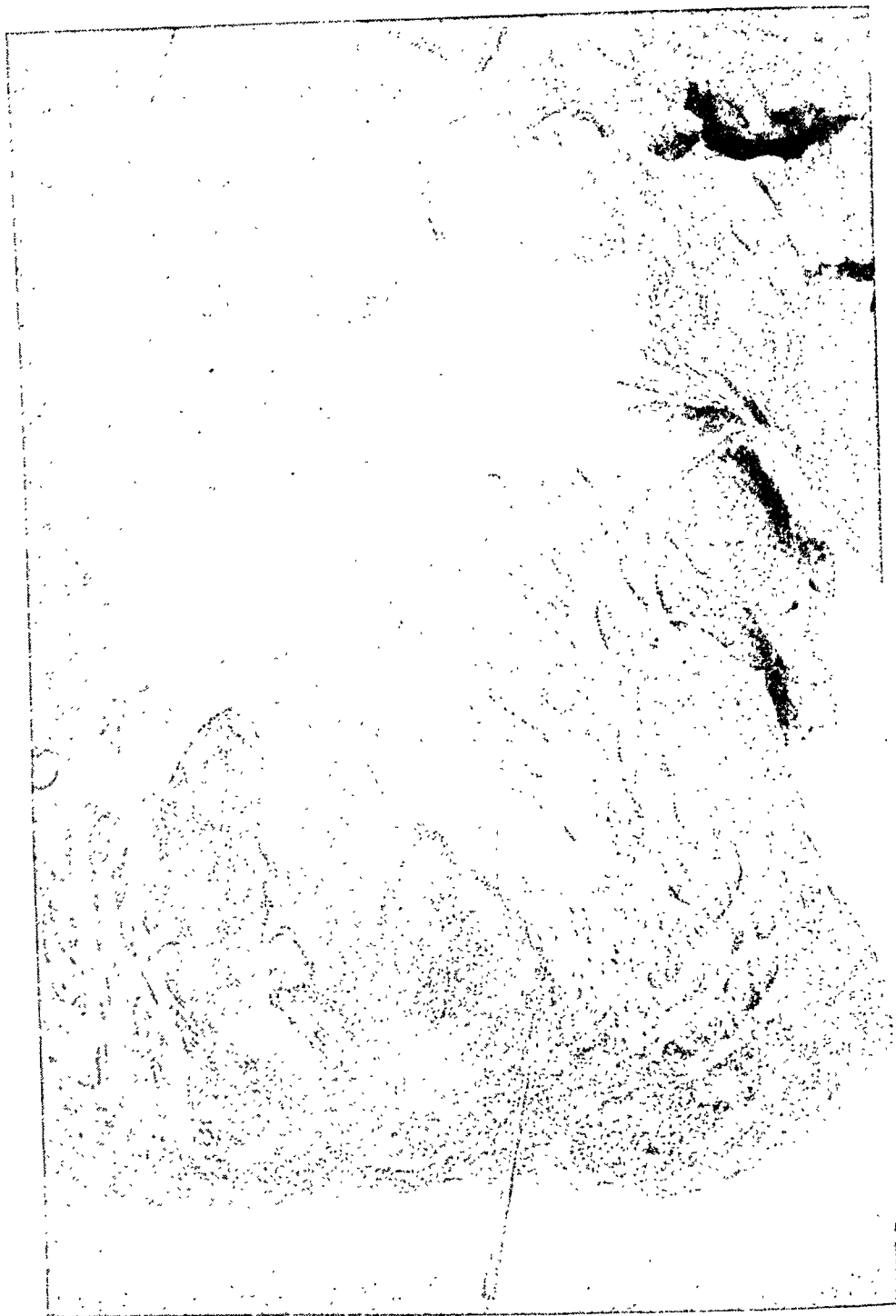


FIG. 2. View of the opened left ventricle showing the mural thrombus, the cut surface of the infarcted apex and probe lying in the septal perforation.

at this time indicated recent anterior myocardial infarction with suggested improvement in conduction in the precordial leads (figure 1b).

On October 9, five days after admission, and eight days following the onset of symptoms, crepitant râles were noted in the right lower lung field posteriorly, and

the patient developed slight dyspnea and non-productive cough. Heart tones were distant; no murmurs were audible. The patient was considered to have developed pulmonary edema incident to left ventricular failure due to recent severe myocardial infarction. Morphine and oxygen were effective in relieving the respiratory distress.

At 7:30 a.m. on October 14, the patient complained of nausea and pain in a rather localized area on the lateral surface of the middle one-third of the left arm.



FIG. 3. Right ventricular view of the septal perforation.

Examination revealed a pulse rate of 126 per minute, fine crepitant râles in both lung bases, and no heart murmurs. Three hours later, on examination by one of us (E. E. I.), the following note was made: "... at this examination the heart is rapid—about 112 per minute. Over the lower sternum there is a loud systolic murmur with occasional premature contractions. With each premature beat a shorter systolic murmur of same timbre as that of the regular beats is heard. Not a friction. Lungs ... a few râles in left lower lateral chest. The right border seems by percussion as previously. Color of lips about same as yesterday (i.e. no cyanosis). No complaint of increased dyspnea. The probability of septal perforation must be considered." The murmur had never before been present, and was so loud that the possibility of its previously having been overlooked was considered untenable. A diagnosis of interventricular septal perforation due to infarction was made on the basis of the sudden appearance of a loud systolic murmur over the lower sternal region in a patient known to have had a recent severe myocardial infarction. No thrill was palpable. An electrocardiogram at this time indicated sinus tachycardia and recent myocardial infarction (figure 1c and d).

The condition of the patient became steadily worse during the following five days, with persistent nausea, marked weakness, and daily increasing evidence of left ventricular failure, as indicated by falling blood pressure, increasing pulmonary edema, rapid weak pulse, and weakening heart tones. Death occurred on October 20, the systolic murmur remaining audible almost to the time of death.

*Pathologic Report* (Dr. George Penick). The heart and aortic arch together weighed 425 gm. The epicardial surface was smooth. The left ventricular wall at the apex was infarcted, as evidenced by soft consistency and greenish-purple discoloration. In the left ventricle there was a mural thrombus measuring from 15 to 30 mm. in thickness, which was adherent to the endocardium of the left lateral wall of the ventricle and the left surface of the interventricular septum (figure 1). At the apex of the septum just anterior to the margin of the thrombus was a perforation which was edged with ragged, necrotic myocardium and which had a maximum diameter of 12 mm. (figures 2 and 3).

The coronary arteries were markedly sclerosed. The circumflex branch of the left artery was tortuous and its intima presented numerous calcified plaques. In spite of these plaques, its lumen averaged about 2 mm. in diameter. Extensive atherosclerosis had narrowed the lumen of the right coronary artery to an average diameter of less than 1 mm. A thrombus occluded the lumen of the anterior descending branch of the left artery at a point 2 cm. from the origin of this branch. Distal to the thrombus, the lumen was filled with coagulated blood for a distance of 2.5 cm. The extent of the infarction was determined by sectioning the formalin-fixed heart. Necrotic myocardium occupied an area 5 cm. square in the apical portion of the anterior wall of the left ventricle. The infarct extended into the inferior 3 cm. of the interventricular septum. Microscopic examination of sections from the area of infarction disclosed degenerating myocardial fibers with extensive intramuscular hemorrhage and a minimal leukocytic reaction, which were superimposed on a healing acute infarct, as evidenced by fibroblastic proliferation in adjacent regions.

Other cardiac findings were an anatomical patency of the foramen ovale and a lipoidal deposition in the cusps of the aortic and mitral valves.

Evidence of myocardial failure was found in an extensive pulmonary edema (overshadowed in the right lower lobe by an acute lobar pneumonia), and in an acute central necrosis of the hepatic lobules, accompanied by sinusoidal congestion and mild, parenchymal, fatty degeneration.

Peripheral embolism, presumably from the mural thrombus, had resulted in three subcapsular acute splenic infarcts. The brain was fixed in formalin and serially sectioned, but no emboli or other lesions were demonstrated.

Generalized, severe, intimal hyalinization was found in the arterioles throughout the viscera. In the kidneys this was accompanied by arterial and arteriolar nephrosclerosis as manifested by a firmly adherent renal capsule, cortical scarring, glomerular hyalinization, and tubular atrophy. Atrophy of a portion of the left renal cortex had resulted from compression by a cyst found in the capsule of this kidney. This cyst measured 5 cm. in diameter and was filled with uncoagulated, semi-solid, dark brown blood.

The other findings are listed below, together with those mentioned in the foregoing paragraphs, and were non-contributory to the clinical course of the patient.

The complete pathologic diagnoses in this case were:

Arteriosclerosis, generalized, severe, with calcification and ulceration. Thrombus, occlusive, in left coronary artery, anterior descending branch, 2 cm. distal to bifurcation. Infarct, acute, of myocardium of left ventricle, anterior wall, and of interventricular septum, apical. Perforation of interventricular septum, secondary to infarction. Thrombus, mural, left ventricular, of septal and lateral walls, adherent, organizing. Patency of foramen ovale, with apposition of primary and secondary septa. Atheromatosis of aortic and mitral valves, moderate. Edema, pulmonary, acute, bilateral, severe. Pneumonia, lobar, acute, right lower lobe. Necrosis, central, acute, congestive, of liver, with mild fatty degeneration. Edema, subcutaneous, of dorsa of feet, mild. Arteriosclerosis, severe, of spleen, pancreas, kidneys, adrenals, thyroid. Nephrosclerosis, arterial and arteriolar, moderate, bilateral. Degeneration, hyalin, of collagen, of renal pyramids. Cyst of renal capsule, left, with hemosiderosis. Atrophy of kidney, left, local, compression. Edema of intima of descending aorta. Infarcts of spleen, anemic, acute, multiple, subcapsular, with associated venous thrombosis and arteritis, acute. Perisplenitis, acute, mild. Hyaline deposits in spleen, corpuscular. Infarct, pulmonary, healed, peripheral, right middle lobe, small. Emphysema, marginal, of left lung, mild. Anthracosis, pulmonary, bilateral, mild. Atrophy, senile, of uterus, Fallopian tubes and ovaries. Cysts, Nabothian, of endocervical canal. Fibrosis of appendix, obliterative. Adhesions, fibrous, peritoneal, between parietal peritoneum and ileum, splenic flexure of colon, sigmoid colon, and between spleen and descending colon. Adhesions, fibrous, pleural, anterior, apical, of left lung. Hydrothorax, left, moderate (250 c.c.). Lipoma, subcutaneous, of left antecubital fossa.

#### COMMENT

The diagnosis of this condition should not be difficult if the possibility is kept in mind, in a patient with a known coronary thrombosis and myocardial infarction, the sudden development of a systolic murmur located over or slightly to the left of the lower portion of the sternum at the fourth and fifth intercostal space is highly suggestive of septal perforation. Myocardial infarction with rupture of a papillary muscle might conceivably cause confusion, although in this the murmurs are reported as more bizarre, less well localized and may be associated with considerable cardiac enlargement.<sup>1</sup> Left ventricular dilatation with systolic murmur is likely to develop more slowly.

The general appearance and condition of the patient were the same as ordinarily seen in infarction without perforation, and death occurred from the severity of the infarction rather than from the fact that the septum incidentally perforated in the process. The average length of life in 10 patients following septal perforation is reported to be between nine hours and seven days, with an average of 2.25 days (Edmondson and Hoxie<sup>3</sup>), although Wood and Livezey<sup>4</sup> report a case of a man 44 years of age who survived five years following septal perforation, ultimately dying in congestive failure.



## SUMMARY

A case of perforation of the infarcted interventricular septum is reported. It is suggested that the diagnosis of such a condition is not difficult if the possibility is kept in mind.

## BIBLIOGRAPHY

1. SAGER, R. V.: Coronary thrombosis: perforation of the infarcted interventricular septum, *Arch. Int. Med.*, 1934, liii, 140.
2. LATHAM, P. M.: Lectures on subjects connected with clinical medicine comprising diseases of the heart, 1847, Ed. Barrington & George D. Haswell, Philadelphia, Lecture xxvi, p. 243.
3. EDMONDSON, H. A., and HOXIE, H. J.: Hypertension and cardiac rupture. A clinical and pathological study of 72 cases, in 13 of which rupture of the interventricular septum occurred, *Am. Heart Jr.*, 1942, xxiv, 719.
4. WOOD, F. C., and LIVEZEY, M. M.: Five year survival after perforation of interventricular septum caused by coronary occlusion: histologic study of kidneys after 350 injections of mercurial diuretics, *Am. Heart Jr.*, 1942, xxiv, 807.
5. STANLEY, D. F.: Acquired interventricular septal defect. Report of a case, *Am. Heart Jr.*, 1937, xiv, 240.
6. SCOTT, R. W., and GARVIN, C. F.: Myocardial infarction with rupture of the septum, report of a case, *Am. Heart Jr.*, 1939, xvii, 375.
7. BAYLEY, R. H., and FADER, D. E.: Ante-mortem diagnosis of rupture of interventricular septum as a result of myocardial infarction, *Am. Heart Jr.*, 1941, xxi, 238.
8. MOOLTON, S. E.: Prolonged survival after perforation of the infarcted interventricular septum in coronary arterial disease, *Arch. Int. Med.*, 1942, lxix, 108.
9. WEBER, M. L.: Perforation of the interventricular septum following infarction; intra-vitam diagnosis. Report of a case and survey of the literature, *Ann. Int. Med.*, 1943, xix, 273.
10. GROSS, H., and SCHWARTZ, S. P.: Acquired interventricular septal defect, *Am. Heart Jr.*, 1936, xi, 626.
11. MASTER, A. M., and RUSSELL, T. B.: Acute coronary artery occlusion with intraventricular septal perforation, Bernheim syndrome, and superior vena cava obstruction, diagnosed clinically, *Ann. Int. Med.*, 1945, xxii, 440.
12. LOBER, P., and HERZOG, A. J.: A case for diagnosis, *Minnesota Med.*, 1945, xxviii, 733.
13. WOOD, A. M.: Perforation of the interventricular septum due to cardiac infarction, *British Heart Jr.*, 1944, vi, 191.
14. KATZ, L. N.: *Electrocardiography*, 1946, Lea & Febiger, Philadelphia.

## EDITORIAL

### *SOME ASPECTS OF ADRENAL CORTICAL FUNCTION AND PITUITARY-ADRENAL RELATIONSHIPS*

IN April, 1949 Hensch et al.<sup>1</sup> reported that the administration of one of the adrenal cortical hormones, 17-hydroxy-11-dehydrocorticosterone (Compound E), produced beneficial effects of a striking nature in a group of patients with advanced rheumatoid arthritis. Withdrawal of the hormone was followed by the recurrence of signs and symptoms of the disease. Essentially similar results were obtained in several patients who were given adrenocorticotrophic hormone (ACTH) derived from hog pituitary. In a subsequent paper<sup>2</sup> these investigators reported that the administration of compound E to three patients with acute rheumatic fever was also followed by rapid subsidence of clinical evidences of the disease. These findings have recently been confirmed by Thorn et al.<sup>3</sup> who have, in addition, reported preliminary observations indicating a beneficial response in several patients with acute disseminated lupus erythematosus and gouty arthritis. Unpublished observations indicate that similar responses have occurred in several disease entities of allergic etiology.

In all these reports, the fact has been stressed that the observations were to be considered as of a preliminary nature. The periods of study have been relatively short. The possible toxic effects of long term administration of these agents have yet to be evaluated. Furthermore, the scarcity and expense of the hormones have precluded widespread and prolonged use. Nevertheless, these reports have not only aroused great interest but have resulted in considerable speculation regarding the mode of action of the agents. They have succeeded also in challenging certain time-honored, even though inadequate, concepts of the pathogenesis of these diseases. Although it is impossible at this time to provide a complete pharmacologic rationale for the action of these hormones, it may, nevertheless, be profitable to examine some of the known metabolic effects of the adrenal cortical steroid hormones as well as some aspects of the pituitary-adrenal relationship.

In a recent report Gaunt and Eversole<sup>4</sup> have provided a brief, but excellent perspective of the entire adrenal cortical problem. Stewart<sup>5</sup> stated

<sup>1</sup> HENCH, P. E., KENDALL, E. C., SLOCUMB, C. H., and POLLEY, H. F.: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis; preliminary report, Proc. Staff Meet. Mayo Clinic, 1949, xxiv, 181.

<sup>2</sup> HENCH, P. E., SLOCUMB, C. H., BARNES, A. R., SMITH, H. L., POLLEY, H. F., and KENDALL, E. C.: The effects of the adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (compound E) on the acute phase of rheumatic fever: preliminary report, Proc. Staff Meet. Mayo Clinic, 1949, xxiv, 277.

<sup>3</sup> THORN, G. W., BAYLES, T. B., MASSELL, B. F., FORSHAM, P. H., HILL, S. R., SMITH, S., and WARREN, J. E.: Studies on the relation of pituitary-adrenal function to rheumatic disease, N. Eng. Jr. Med., 1949, ccxli, 529.

<sup>4</sup> GAUNT, R., and EVERSOLE, W. J.: Notes on the history of the adrenal cortical problem, Ann. N. Y. Acad. Sci., 1949, I, 511.

<sup>5</sup> STEWART, G. N.: Adrenalectomy and the relation of the adrenal body to metabolism, Physiol. Rev., 1924, iv, 163.

in 1924 that although the available evidence indicated that the adrenal cortex was essential to life, knowledge as to how it functioned was quite unknown. The information was fragmentary and did not lend itself to unification. As late as 1930 Britton<sup>6</sup> stated that the meagerness of knowledge regarding cortico-adrenal function still did not permit rational theorizing. The modern history of adrenal cortex function may be said to have started in 1930 for it was in that year that Swingle and Pfiffner<sup>7</sup> were able to prepare the first good adrenal cortical extract. The first clinical trial of this material in Addison's disease occurred in the same year. It was assumed, at first, that only one cortical hormone existed. By 1936 various workers had demonstrated that a large number of steroid hormones could be crystallized from the adrenal cortex. In all, some 28 steroid hormones have been isolated from cortical extracts.<sup>8</sup> Six of these (*vide infra*) have been found to be capable of maintaining life in the adrenalectomized animal. Most investigators report the existence of an amorphous fraction which remains in their extracts after known steroids have been removed and which is highly active in maintaining life, but whose metabolic activities are but little understood. The only adrenal steroid for which a satisfactory and cheap method of synthesis became available early was desoxycorticosterone, customarily used as its acetate (DCA). This hormone was found to exert a profound effect on inorganic metabolism and to be quite potent in maintaining the life of patients with Addison's disease. Yet it is found only in very small quantities in the adrenal cortex. Great difficulties were encountered until recently in finding methods for the synthetic production of other adrenal steroids. The recent discovery by Kendall of an effective, if not cheap, method of partial synthesis is an important event in adrenal history.<sup>9</sup>

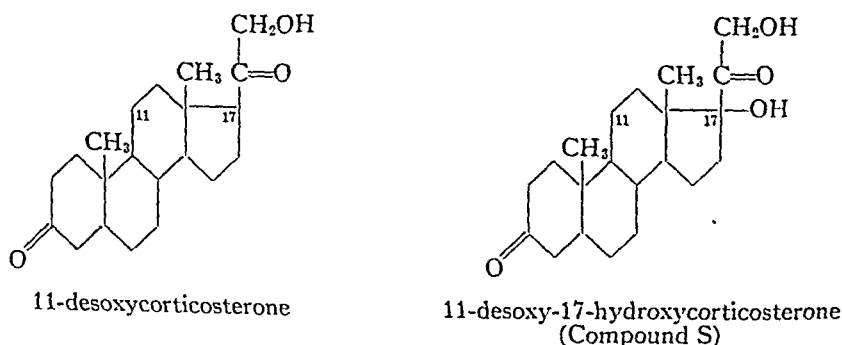


FIG. 1

The corticosteroids which lack oxygen at Carbon-11. The major effect of these compounds is upon inorganic metabolism.

<sup>6</sup> BRITTON, S. W.: Adrenal insufficiency and related considerations, *Physiol. Rev.*, 1930, x, 617.

<sup>7</sup> SWINGLE, W. W., and PFIFFNER, J. J.: An aqueous extract of the suprarenal cortex which maintains the life of bilaterally adrenalectomized cats, *Science*, 1930, lxxi, 321.

<sup>8</sup> REICHSTEIN, T., and SHOPPEE, C. W.: The hormones of the adrenal cortex—in vitamins and hormones, Academic Press, Inc., New York, Vol. 1, p. 345.

<sup>9</sup> KENDALL, E. C.: The chemistry and partial synthesis of adrenal steroids, *Ann. N. Y. Acad. Sci.*, 1949, I, 540.

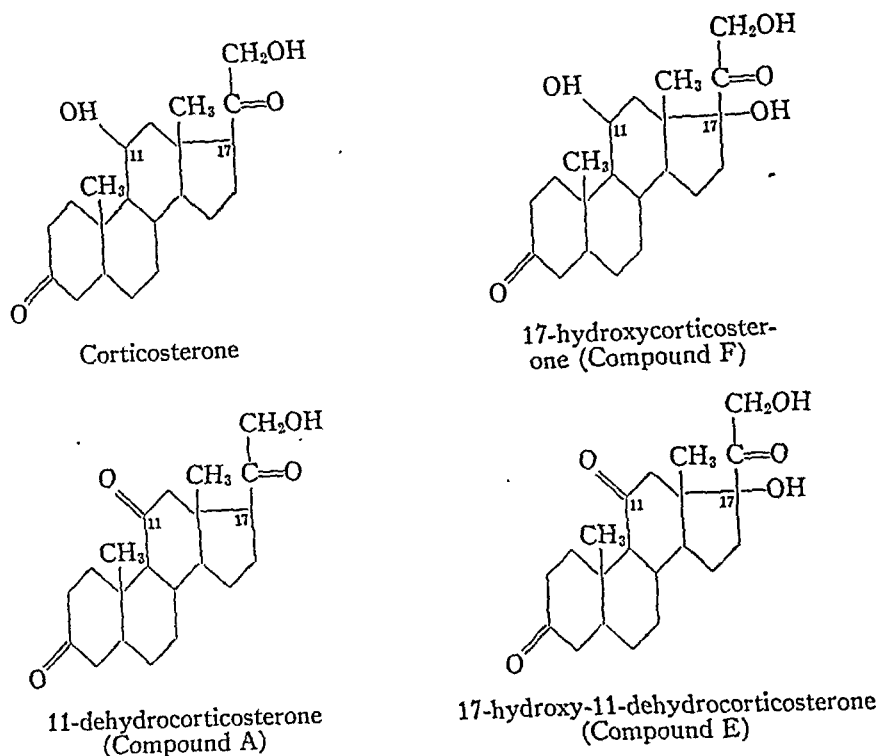


FIG. 2

The corticosteroids oxygenated at Carbon 11. These have a predominant effect on organic metabolism.

It is now known that the adrenal cortical steroids fall into three groups with reference to their physiological activity, namely, those which have a predominant effect on electrolyte and fluid balance, those which are concerned primarily with the intermediary metabolism of protein and carbohydrate, and those which have an androgenic and anabolic effect.<sup>10</sup> Any attempt to provide a concise summary of the rôle played by these steroids in physiological processes involves a great risk of oversimplification. Furthermore, it should be pointed out that there is experimental evidence of overlapping of functions between these groups. The lack of exact knowledge of the metabolic functions of the amorphous fraction leaves an unavoidable gap in any presentation of the subject at this time. With these limitations in mind a brief summary of the available information can be attempted.

For greater clarity of understanding the structural formulae of the six steroids which possess biological activity are presented (figures 1 and 2). It will be observed that the major difference between the two groups consists in the absence of an oxygen molecule (desoxy-) at Carbon 11 in the first group and its presence, in either keto- or hydroxy form, at Carbon 11 in the second group. The first group are known collectively, as desoxycorticosterones, while the latter are referred to as corticosterones. The adrenal

<sup>10</sup> SWINGLE, W. W., and REMINGTON, J. W.: The rôle of the adrenal cortex in physiological processes, *Physiol. Rev.*, 1944, xxiv, 89.

steroids with androgenic activity are related in structure to testosterone but carry an oxygen molecule in position eleven (androsterone).

The desoxycorticosterones exert a regulatory effect on electrolyte and fluid balance by (1) acting directly upon the renal tubules, allowing them to conserve sodium and water and release potassium; (2) in a not-too-clear manner, determining fluid and electrolyte partitioning across cell membranes, capillary endothelium, and intestinal mucosa; (3) influencing sodium and potassium metabolism and thereby producing secondary effects upon extra- and intracellular hydration.

The oxygenated C-11 steroids are concerned primarily with the intermediary metabolism of protein and carbohydrate. Recent work has also demonstrated that these steroids exert a very definite effect upon the hematopoietic system, the details of which are considered below. Carbohydrate metabolism is influenced in the following general ways: (a) the corticosterones increase the conversion of fed carbohydrate to glycogen; (b) they influence the conversion of endogenous protein to glycogen (gluconeogenesis) by assisting either in the process of deamination of amino acids or in the conversion of keto- and hydroxy acids to carbohydrate; (c) they diminish the oxidation of available carbohydrate.

Despite the enormous amount of work which has been done during the past several years, the details of the reactions into which the cortical hormones enter to bring about these metabolic effects are quite unknown. One must not confuse end results, such as those mentioned above, with the processes of action. In general, adrenal cortical deficiency leads to a disturbance in energy metabolism characterized by general "asthenia" of all the tissues, organs and organ systems which is reflected in a failure of the work capacity of the skeletal muscles, disturbance in certain renal functions, failure of lactation, decreased ability of the vasculature to withstand even minor stresses, and increased sensitivity of the organism as a whole to certain drugs and toxins. Recent work strongly suggests that hyperadrenocorticism manifests itself in a manner resembling Cushing's syndrome.<sup>11</sup>

It has become increasingly evident that the major regulatory factor of adrenal cortical function is the anterior pituitary. This regulation is achieved through the secretion of adrenocorticotrophic hormone (ACTH). Long<sup>12</sup> states that as far as can be determined, all circumstances which enhance the secretion of the adrenal cortex can only do so by first activating the anterior lobe of the pituitary in consequence of which the required quantity of ACTH is released. It has long been known that hypophysectomy is followed by atrophy of the adrenal cortex, but not of the medulla. This atrophy can be prevented or the involuted glands restored to a normal condition by the administration of anterior lobe extracts. In 1933 Collip<sup>13</sup> reported the iso-

<sup>11</sup> KEPLER, E. J.: Cushing's disease: a primary disorder of the adrenal cortices?, *Ann. N. Y. Acad. Sci.*, 1949, 1, 657.

<sup>12</sup> LONG, C. N. H.: Conditions associated with secretion of adrenal cortex, *Federation Proc.*, 1947, vi, 461.

<sup>13</sup> COLLIP, J. B., ANDERSON, E. M., and THOMSON, D. L.: The adrenotropic hormone of the anterior pituitary lobe, *Lancet*, 1933, ii, 347.

lation, in impure form, of adrenocorticotrophic hormone. However, it was not until 1943 that a pure form of the hormone, unadulterated by other secretions of the gland, was obtained by several groups of investigators.<sup>14, 15</sup> Since that time it has become possible, with greater precision, to study pituitary-adrenal relationships. In a manner common to other glandular interrelationships, there is apparently an internal self-regulatory mechanism between the adrenal cortex and the anterior pituitary. Increased concentration of corticosteroids in the circulating blood has an inhibitory effect upon the secretion of ACTH while a diminished quantity of the adrenal hormones results in antithetical activity.

The administration of ACTH is followed by striking morphological and biochemical changes in the adrenals of several animal species.<sup>16</sup> The biochemical changes largely concern the concentration of cholesterol and ascorbic acid. The adrenals contain a high concentration of cholesterol which is in a labile state. The administration of a single dose of ACTH results, within 3 hours, in a 50 per cent drop in the concentration of cholesterol in the gland. By the end of 24 hours the concentration of this substance has returned to normal. During the period of cholesterol depletion evidences of increased cortical hormone activity may be observed. Although no direct evidence exists as yet it is believed that the cholesterol is utilized in the formation of steroid hormones. Simultaneous depletion of the ascorbic acid content of the adrenal occurs after ACTH administration. This substance likewise reaccumulates to a normal concentration within 24 hours. The extremely sensitive response of adrenal ascorbic acid to ACTH is now utilized as a means of bioassay of ACTH potency. The exact relationship between ascorbic acid and the corticosteroids has not yet been established. The most striking morphologic change observed in the glands is hypertrophy. Sayers has stressed the fact that the reactions mentioned above must be looked upon as dynamic mechanisms which produce varying results depending upon the intensity and duration of the stimulus.

The significance of these observations is underscored by the fact that similar biochemical and morphological changes can be induced in the adrenals by a variety of situations which subject the animal to stress. Among the experimentally induced stress situations have been acute hemorrhage, exposure to extreme cold, scalding, stimulation of sensory nerves, operative procedures, injection of killed *B. coli*, and simulated altitudes of 20,000 feet. A variety of drugs, including histamine, epinephrine, ether, chloroform, etc., can also produce these effects. Similar treatment of previously hypophysectomized rats fails to produce a reduction of the cholesterol and ascorbic acid content of the adrenals. Long<sup>12</sup> believes that the common denominator

<sup>14</sup> LI, C. H., EVANS, H. M., and SIMPSON, M. E.: The adrenocorticotrophic hormone, Jr. Biol. Chem., 1943, cxlix, 413.

<sup>15</sup> SAYERS, G., WHITE, A., and LONG, C. N. H.: Preparation and properties of pituitary adrenotropic hormone, Jr. Biol. Chem., 1943, cxlix, 425.

<sup>16</sup> SAYERS, G., and SAYERS, M. A.: The pituitary-adrenal system, Ann. N. Y. Acad. Sci., 1949, lv, 522.

which occurs in all of these situations is an excitation of the autonomic nervous system with the release of its specific hormone, epinephrine. Epinephrine injected subcutaneously, intravenously or intramuscularly can produce cholesterol and ascorbic acid depletion of the adrenals. This effect is abolished in the hypophysectomized rat. Furthermore, the previous administration of cortical hormones to the rat inhibits the reduction in adrenal cholesterol and ascorbic acid content presumably as a result of diminished ACTH production.

Several groups of investigators<sup>17, 18, 19</sup> have recently studied the effect of ACTH administration in man. Some studies were made after administration of a single dose of 25 mg. while others were done during a control period of 4-6 days during which the subjects received 40 mg. per day in divided doses. The results observed in normal individuals fall into several categories. There are a number of characteristic hematologic changes which include an average drop in the total eosinophile count of 75 per cent, an average drop of 45 per cent in lymphocytes, and an average increase in neutrophils of 98 per cent. The metabolic changes observed included increased urinary excretion of uric acid, 17-ketosteroids, and potassium. Slight increase in fasting blood sugar levels occurred as well as slight increase in liver glycogen as determined by biopsy. There was also slight increase in body weight and striking decrease in the excretion of sodium. There was no significant elevation in either the diastolic or systolic blood pressures. No increase in the globulin content of the serum occurred nor was there any measurable antibody increase. These changes, in the aggregate, suggested that there had been stimulation of secretion of all the cortical steroids. In patients with Addison's disease these effects could not be produced after the administration of ACTH. Similar effects could, however, be produced in Addisonians by the injection of compound F. Desoxycorticosterone administered to Addisonians failed to produce the characteristic hematologic changes. It appears that these are mediated through the corticosterones.

A recent report by Hume presents evidence that the anterior hypothalamus constitutes an important link in the reaction of the body to stress. By producing localized lesions in a specific area of the hypothalamus, the formation of ACTH could be inhibited after stimuli which were ordinarily adequate for this purpose.

In the alarm reaction of Selye,<sup>21</sup> induced by a large variety of stress sit-

<sup>17</sup> FORSHAM, P. H., THORN, G. W., PRUNTY, F. T. G., and HILLS, A. G.: Clinical studies with pituitary adrenocorticotropin, *Jr. Clin. Endocrin.*, 1948, viii, 15.

<sup>18</sup> MASON, H. L., POWER, M. H., RYNEARSON, E. H., CIARAMELLI, L. C., LI, C. H., and EVANS, H. M.: The results of administration of anterior pituitary adrenocorticotrophic hormone to a normal human subject, *Jr. Clin. Endocrin.*, 1949, viii, 1.

<sup>19</sup> SAYERS, G., BURNS, T. W., TYLER, F. H., JAGER, B. V., SCHWARTZ, T. B., SMITH, E. L., SAMUELS, H. T., and DAVENPORT, H. W.: Metabolic actions and fate of intravenously administered adrenocorticotrophic hormone in man, *Jr. Clin. Endocrin.*, 1949, ix, 593.

<sup>20</sup> HUME, D. M.: The rôle of the hypothalamus in the pituitary-adrenal cortical response to stress, *Jr. Clin. Invest.*, 1949, xxviii, 790.

<sup>21</sup> SELYE, H.: The general adaptation syndrome and the diseases of adaptation, *Jr. Clin. Endocrin.*, 1946, vi, 117.

uations, active participation of the anterior pituitary and adrenal cortex occupies a position of central significance. Selye has pointed out that the alarm reaction, however, is only one aspect, i.e. the first stage, of a syndrome which he calls the general adaptation syndrome. The other phases are the stage of resistance and the stage of exhaustion. In a comprehensive review, this investigator discusses the possibility that a variety of diseases such as hypertension, nephrosclerosis, rheumatic fever, and rheumatoid arthritis, to mention but a few, may be "diseases of adaptation" resulting from excessive or abnormal adaptive efforts involving the pituitary-adrenal system. With the expectation of an increased availability of purified hormones in the not too distant future these important concepts should offer fruitful sources for further intensive experimental investigation.

M. S. S.



## REVIEWS

*Arthritis and Allied Conditions.* 4th Ed. By the late BERNARD I. COMROE, M.D.; completely revised and rewritten by JOSEPH L. HOLLANDER, M.D., and collaborators. 1108 pages. 16 × 24 cm. 1949. Lea and Febiger, Philadelphia. Price, \$16.00.

Since Dr. Comroe's untimely death, advances in the field of rheumatism have made a revision of his standard work on arthritis inevitable. This has been undertaken and effected by a team of 17 leading rheumatologists. It is a tribute to Dr. Comroe's original work that much of its character and content graces the present edition.

The type has been somewhat compressed and, despite the inclusion of much new material, the present volume is shorter than the last edition by 250 pages. New chapters have been added on Joint Physiology, Rehabilitation of the Arthritic Patient, the Collagen Diseases, Rarer Forms of Metabolic Arthritis, Pregnancy in Arthritis and Reiter's Syndrome; and many new sections, such as those on the Shoulder-Hand Syndrome, Psychogenic Rheumatism, Normal Aging of Joints and Osteoporosis, have been included.

The editors have retained and increased the number of "summaries in box form" which have proved so valuable to those who have limited reading time and who use this book mainly as a work of reference. Often these are not true summaries, in that there is more information contained in them than in the relevant body of the text. For example the paragraph dealing with vaccines in the treatment of rheumatoid arthritis contains but 30 words, while the "summary" of the subject boasts over 130. This seems to represent a strange inversion.

Though this is undoubtedly a good text it is not as good as it should be. The large number of misprints and the many unnecessary repetitions in the text suggest to the reader hasty proof-reading and indifferent editing. The virtue of multiple authority has also the disadvantage of admitting contradictions.

It shows commendable enterprise to include reference to the new hormonal theory and therapy of rheumatoid arthritis. But one gets a little tired of seeing every allusion to adrenal cortical insufficiency, ACTH and substance E, paraded in italics or heavy black type. It may well prove, with time, to be the most significant of arthritic topics, but at the moment it is still the newest; and news is never as bad or as good as it sounds when it is first heard. It is too early to wave this flag so vigorously from the high eminence of a standard textbook.

The book is excellently illustrated with 370 figures including 160 new ones; it contains a wealth of practical detail and a large and up to date bibliography. As well as covering the entire field of rheumatology, many clinical entities, which seem far removed from arthritis but which can simulate "rheumatism" (sarcoidosis, bone tumors, scleroderma, and others), are well and fully discussed. These and many other good features make this authoritative publication a most useful encyclopedia of the rheumatic diseases. All in all it should justify the editors' hope that it will prove of value and interest to a wide variety of physicians.

H. J. L. M.

*Textbook of Medicine.* 8th Ed. By various authors; edited by SIR JOHN CONYBEARE, K.B.E., M.C., D.M. Oxon., F.R.C.P. 1170 pages; 22.5 × 14.5 cm. Williams and Wilkins Co., Baltimore. 1946. Price, \$8.00.

This "Textbook of Medicine" is compiled from the efforts of many contributors and is divided into 19 sections. The first section is entitled "Infectious Diseases"

but is incomplete since the following three sections on "Tuberculosis," "Venereal Disease" and "Tropical Diseases" should be included under this heading. It seems misleading to classify such diseases as bacillary dysentery, amebic dysentery, typhus fever, rabies, malaria, and "effects of heat" as tropical diseases. Certainly, they are all illnesses found in nontropical areas, and it is unfair to stress them as regional diseases, especially to students. The pneumonias are separately grouped under "Diseases of the Lungs."

There is a section on the Diseases of Infants. Rickets is discussed in this section. The other vitamin deficiency diseases are included under "Diseases of Metabolism." There is no mention of vitamin A deficiency.

The subject matter is often handled with such brevity as to render it useless to all intent and purpose. So far as the reviewer can determine, no mention is made of tularemia, torulosis, ornithosis, acute arteritis, toxoplasmosis, porphyria, Haverhill fever, and splenic neutropenia.

This textbook is not impressive in either its organization or content.

E. C.

*An Atlas of Electrocardiography.* By WILLIAM DRESSLER, M.D., Cardiologist, Maimonides Hospital, Brooklyn, Consultant in Cardiology, The Brooklyn Hospital, Lecturer in Medicine, Long Island College of Medicine; and HUGO ROESLER, M.D., F.A.C.P., Cardiologist, Department of Medicine, Associate Professor of Radiology, Temple University Medical School and Hospital. 503 pages, 27.5 x 21 cm. Charles C. Thomas, Springfield, Ill. 1949. Price, \$14.00.

This atlas is intended for those already conversant with the fundamentals of electrocardiography. Section I deals with electrocardiographic patterns excluding rhythm disturbances. Section II is devoted to disturbances of rhythm. Section III is concerned with advances in the electrocardiographic diagnosis of myocardial infarction. Section IV is a short section on unipolar leads.

In the first two sections, tracings which display similar patterns are arranged together, and the differential diagnosis is discussed. A summary of the clinical data is presented in addition to the electrocardiographic comment. This arrangement is valuable for teaching purposes and is commended. The section on disturbances of heart rhythm is especially good.

Most of the precordial leads shown are CF or CR; there are comparatively few records with V leads. The discussion of inverted T waves in Lead III makes no mention of variation of  $T_3$  with respiration, and no example of this common finding is shown. Statements are made concerning the localization of myocardial damage which are based upon the electrocardiograms shown, which in some instances are such that pathological confirmation would seem desirable. The records interpreted as indicating anterior myocardial infarction in the presence of left bundle branch block are very interesting, and would prove more valuable were postmortem studies available. The authors devote a good deal of space to records with the " $T_1$  smaller than  $T_3$ " pattern. They state that notching of T is probably equivalent to inversion of T. There are occasional references to certain electrocardiographic findings as reflecting "a positional peculiarity of the heart"; but more specific details of position or supporting information are not presented.

This text generally is interesting and informative, and possesses many virtues. These overshadow minor faults, which will probably disappear in future editions.

S. S.

*Clinical Biochemistry.* 4th Ed. By ABRAHAM CANTAROW, M.D., Professor of Biochemistry, Jefferson Medical College; and MAX TRUMPER, Ph.D., Commander, H(S), USNR., Lecturer in Clinical Biochemistry and Basic Science Coördinator, Naval Medical School, National Naval Medical Center, Bethesda, Md. 642 pages; 15.5 × 24 cm. W. B. Saunders Co., Philadelphia. 1949. Price, \$8.00.

In this edition of "Clinical Biochemistry," as well as in the earlier editions, the authors have applied current biochemical knowledge to problems in the diagnosis and treatment of disease. The chapters which have been revised include: renal and respiratory regulation of acid-base balance; pigment metabolism in relation to jaundice; carbohydrate, lipid and protein metabolism; thyroid function; absorption and storage of iron; action of parathyroid hormone; renal physiology; vitamins; experimental diabetes. A number of new topics have also been added.

Although this edition should serve as a good reference volume, the apparent attempt to limit the size to that of the previous editions appears to have been a handicap in the discussion of some of the material while some topics of relatively little current interest are still included. The bibliography is extensive but includes relatively few references later than 1945.

M. A. A.

*Cardiovascular Disease.* By LOUIS H. SIGLER, M.D., F.A.C.P., Attending Cardiologist and Chief of Cardiac Clinic, Coney Island Hospital; Consulting Cardiologist, Rockaway Beach Hospital and Menorah Home and Hospital for the Aged. 551 pages, 15.5 × 23.5 cm. Grune & Stratton, New York. 1949. Price, \$10.00.

This new book contains chapters on most topics usually covered in other textbooks on cardiovascular disease. Often explanations of cardiac mechanisms are incomplete or are abruptly terminated with such statements as "the mechanism (auricular flutter with varying block) is fully discussed elsewhere," or "the mechanism (interference dissociation) has been fully described elsewhere," or "the reasons for these differences are given elsewhere." In each instance "elsewhere" is a reference to the author's textbook of electrocardiography. The rôle of the electrocardiogram in the diagnosis of myocardial infarction is covered with the statement. "The most important single aid in the diagnosis of coronary occlusion is the electrocardiogram. A complete discussion of the electrocardiographic diagnosis of myocardial infarction is given elsewhere." As for angina pectoris, "Electrocardiographic findings, described elsewhere, may also help in arriving at a diagnosis." It is recommended that one try to discover the presence of a hyperactive carotid sinus reflex as "an important aid in the diagnosis of the anginal syndrome due to coronary sclerosis." "A person who develops coronary occlusion which results in no myocardial damage should be allowed out of bed after three or four days of careful follow-up and the demonstration of the absence of such damage." Details as to how a diagnosis of coronary occlusion with no myocardial damage may be established in that length of time are not presented.

Careful examination of this volume reveals no compelling reason why it should replace the standard texts on this subject.

S. S.

#### BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later but it is not possible to discuss all of them.

*Behandlung innerer Krankheiten: Richtlinien und Ratschläge für Studierende und Ärzte.* By PROF. DR. FERDINAND HOFF. 471 pages; 24.5 × 17.5 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, geb. DM 25.—

*Bentley's Text-book of Pharmaceutics.* 5th ed. Revised by HAROLD DAVIS, B.Sc., Ph.D. (Lond.), Ph.C., F.R.I.C., Pereira Medallist, Sometime Chief Pharmacist, University College Hospital, London, with the collaboration of M. W. PARTRIDGE, B.Pharm., B.Sc., Ph.D. (Lond.), Ph.C., Lecturer in Chemistry, University of Nottingham, and A. I. ROBINSON, Ph.C., Late Pharmacist in Charge, Manufacturing Laboratory, Messrs. Stafford Allen & Sons, Ltd., London, with contributions by W. A. BROOM, B.Sc. (Lond.), F.R.I.C., M. ELLIS, M.Sc. (Wales), F.L.S., and H. A. TURNER, B.Sc. (Lond.), Ph.C., D.B.A. (Pharm. Soc.), Pereira Medalist. 1100 pages; 22.5 × 14.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$7.50.

*Clinical Biochemistry.* 4th ed. By ABRAHAM CANTAROW, M.D., Professor of Biochemistry, Jefferson Medical College, etc., and MAX TRUMPER, Ph.D., Commander, H(S), USNR., Lecturer in Clinical Biochemistry and Basic Science Coordinator, Naval Medical School, National Naval Medical Center, Bethesda, Maryland. 642 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$8.00.

*Fundamentals of Otolaryngology: A Textbook of Ear, Nose and Throat Diseases.* By LAWRENCE R. BOIES, M.D., Clinical Professor of Otolaryngology, Director of Division of Otolaryngology, University of Minnesota Medical School, and Associates: CHARLES E. CONNOR, M.D., ANDERSON C. HILDING, M.D., JEROME A. HILGER, M.D., JOHN J. HOCHFILZER, M.D., CONRAD J. HOLMBERG, M.D., KENNETH A. PHELPS, M.D., ROBERT E. PRIEST, M.D., and GEORGE M. TANGEN, M.D. 443 pages; 24 × 15.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$6.50.

*Gemeinsame Erkrankungen aus der inneren Medizin und Chirurgie.* By WALTHER KANERT and KURT AUGUST KOELSCH. 500 pages; 24.5 × 17.5 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, geb. DM 35.—

*Hemorrhagic Disorders: A Guide to Diagnosis and Treatment.* By PAUL M. AGGELER, M.D., Assistant Clinical Professor of Medicine, and S. P. LUCIA, M.D., Professor of Medicine, University of California Medical School. Lettered and illustrated by PHYLURIA GIBBS, HELENE CLEARE and JEAN THOMPSON, under the supervision of RALPH SWEET. 112 pages; 28 × 22 cm. 1949. The University of Chicago Press, Chicago. Price, \$10.00.

*Lehrbuch der inneren Medizin.* By DR. ERNST LAUDA. 569 pages; 25 × 17.5 cm. 1949. Springer-Verlag, Vienna. Price, \$7.20.

*Medical Clinics on Bone Diseases: A Text and Atlas.* 2nd ed. By I. SNAPPER, M.D., formerly Professor of Medicine, University of Amsterdam, The Netherlands, etc. 308 pages; 28.5 × 22 cm. 1949. Interscience Publishers, Inc., New York. Price, \$20.00.

*Medizin in Bewegung: Klinische Erkenntnisse und ärztliche Aufgabe.* By RICHARD SIEBECK. 520 pages; 24.5 × 17 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, geb. DM 27.—

*Memories of Eighty Years.* By JAMES B. HERRICK. 270 pages; 23 × 15.5 cm. 1949. The University of Chicago Press, Chicago. Price, \$5.00.

*Nervous and Neurohumoral Regulation of Intestinal Motility.* By W. B. YOUMANS, Professor of Physiology, University of Oregon Medical School. 129 pages; 24 × 15.5 cm. 1949. Interscience Publishers, Inc., New York. Price, \$4.75.

- The 1949 Year Book of Medicine (July, 1948–May, 1949)*. Edited by PAUL B. BEESON, M.D., J. BURNS AMBERSON, M.D., GEORGE R. MINOT, M.D., S.D., F.R.C.P. (Edinburgh and London), WILLIAM B. CASTLE, M.D., S. M. (Hon.) Yale, M.D. (Hon.) Utrecht, TINSLEY R. HARRISON, M.D., and GEORGE B. EUSTERMAN, M.D. 831 pages; 18.5 × 12.5 cm. 1949. Year Book Publishers, Inc., Chicago. Price, \$4.50.
- Operations of General Surgery*. 2nd ed. By THOMAS G. ORR, M.D., Professor of Surgery, University of Kansas School of Medicine. 890 pages; 27 × 19 cm. 1949. W. B. Saunders Company, Philadelphia. Price, \$13.50.
- Pharmaceutical Compounding and Dispensing*. Editor-in-Chief: RUFUS A. LYMAN, M.D., Dean, College of Pharmacy, University of Arizona. Advisory Editors: JAMES M. DILLE, Ph.D., ANDREW G. DUMEZ, Ph.D., GLENN L. JENKINS, Ph.D., RUDOLPH A. KUEVER, Ph.C., HUGH C. MULDOON, D.Sc., and HOWARD C. NEWTON, Pharm.D. Technical Editor: GEORGE URDANG, Ph.G., D.Sc. Nat. 321 pages; 26 × 18 cm. 1949. J. B. Lippincott Company, Philadelphia. Price, \$6.50.
- Physiology in Diseases of the Heart and Lungs*. By M. D. ALTSCHULE, Assistant Professor of Medicine, Harvard Medical School, etc. 368 pages; 21.5 × 14.5 cm. 1949. Harvard University Press, Cambridge. Price, \$5.00.
- Physiology in Health and Disease*. 5th ed. By CARL J. WIGGERS, M.D., D.Sc., F.A.C.P., Professor of Physiology and Director of Physiology Department in the School of Medicine of Western Reserve University, Cleveland. 1242 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, \$10.00.
- Pollen-Slide Studies*. By GRAFTON TYLER BROWN, M.D., F.A.C.P., Instructor in Clinical Medicine, Georgetown University School of Medicine, etc. With a Foreword by WALLACE M. YATER, M.D., M.S. (in Medicine), F.A.C.P., Director, Yater Clinic, etc. 122 pages; 23.5 × 15.5 cm. 1949. Charles C. Thomas, Publisher, Springfield, Illinois. Price, \$6.00.
- Principles of Human Physiology, Originally written by Prof. E. H. Starling, M.D., F.R.C.P., C.M.G., F.R.S.* 10th ed. By C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. Birmingham, Jodrell Professor of Physiology in University College, London. The Chapters on the Special Senses by H. HARTRIDGE, M.A., M.D., ScD., F.R.S., Director of Vision Research Unit (Medical Research Council), Institute of Ophthalmology, London. 1193 pages; 25 × 16 cm. 1949. Lea & Febiger, Philadelphia. Price, \$10.00.
- Reports on Biological Standards. III. Methods of Biological Assay Depending on a Quantal Response*. Medical Research Council Special Report Series No. 183. By J. H. GADDUM. 48 pages; 24.5 × 15 cm. (paper-bound). 1933; reissued May 31, 1949. His Majesty's Stationery Office, London. Price, one shilling net.
- Stedman's Medical Dictionary*. 17th revised ed. Edited by NORMAN BURKE TAYLOR, M.D., F.R.S.C., F.R.C.S. (Edin.), F.R.C.P. (Can.), M.R.C.S. (Lon.), University of Western Ontario, etc.; in collaboration with ALLEN ELLSWORTH TAYLOR, D.S.O., M.A. 1361 pages; 24 × 16 cm. 1949. The Williams and Wilkins Company, Baltimore. Price, \$8.50 with thumb index; \$3.00 without thumb index.
- Streptomycin and Dihydrostreptomycin in Tuberculosis: Reports of Research Including Studies Sponsored by the American Trudeau Society (Medical Section, National Tuberculosis Association)*. Edited by H. McLEOD RIGGINS, M.D., and H. CORWIN HINSHAW, M.D. 554 pages; 23.5 × 16 cm. 1949. National Tuberculosis Association, New York. Price, \$7.50.

- Subalimentación crónica y Esprue.* By DR. ARSACIO PEÑA YÁÑEZ. 189 pages; 25.5 × 18 cm. (paper-bound). 1949. Editorial Científico Medica, Barcelona, Spain.
- A Synopsis of Medicine.* 9th ed. By SIR HENRY LETHBY TIDY, K.B.E., M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (Lond.), Extra Physician to H.M. The King, etc. 1243 pages; 19 × 12.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$7.50.
- A Text-book of Pharmacognosy.* 5th ed. By GEORGE EDWARD TREASE, B.Pharm., Ph.C., F.R.I.C., F.L.S., Reader in Pharmacognosy and Head of the Department of Pharmacy in the University of Nottingham. Revised with the assistance of H. O. MEEK, Ph.C., H. E. STREET, B.Sc., Ph.D., Ph.C., and E. O'F. WALSH, B.Sc., Ph.D., A.R.I.C., Ph.C. 811 pages; 22.5 × 14.5 cm. 1949. The Williams and Wilkins Company, Baltimore. Price, \$8.00.
- Tom Cullen of Baltimore.* By JUDITH ROBINSON. 435 pages; 23.5 × 16 cm. 1949. Oxford University Press, New York. Price, \$3.50.
- Von der Angst der Kranken.* By PROF. DR. MED. KARL SCHEELE. 76 pages; 21 × 14.5 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart. Price, kart. DM 4.80.
- A Year With Osler—1896—1897. Notes taken at his Clinics in The Johns Hopkins Hospital.* By JOSEPH H. PRATT, a Member of the Class of 1898. 209 pages; 23.5 × 15.5 cm. 1949. The Johns Hopkins Press, Baltimore. Price, \$4.00.

# COLLEGE NEWS NOTES

## THE 1949 DIRECTORY OF THE COLLEGE

The new and revised Directory of the American College of Physicians is expected off press, ready for mailing to all who placed orders, before the end of the year. The forms closed on October 1, 1949, and thus the Directory will not contain additions to its membership after that date. The price to members of the College is \$4.00, post-paid; to non-members and institutions, \$5.00. Those who have previously placed their orders will receive statements after delivery of the Directory.

---

### GIFT TO THE COLLEGE LIBRARY

Dr. S. T. Laufer, F.A.C.P., Halifax, Nova Scotia, recently presented to the Library of the American College of Physicians a very old manuscript, entitled (as translated), "Clinical Medicine," which was written in longhand and in Latin at Naples, Italy, in 1709, by Nicholaus Corazzelli. It is an orderly book following amazingly closely current case reports and medical texts. It gives the title of the disease, its recognized symptoms and causes, the diagnosis, prognosis and treatment. It is interesting to find in a manuscript prepared so long ago so many diseases then recognized and named, the names persisting to the present time.

---

### A.C.P. POSTGRADUATE COURSES

The following postgraduate courses offered by The American College of Physicians on its Autumn, 1949, schedule are the only ones remaining open for registration:

#### COURSE NO. 7—BLOOD DYSCRASIAS

(December 6-10, 1949)

MEDICAL COLLEGE OF ALABAMA

BIRMINGHAM, ALA.

JAMES B. McLESTER, M.D., F.A.C.P., *Director*

Fees: A.C.P. Members, \$30.00  
V. A. (P. L. 346), \$30.00  
Non-members, \$60.00

#### OFFICERS OF INSTRUCTION

*Medical College of Alabama*

ROY R. KRACKE, M.D., Dean and Professor of Clinical Medicine.

ROGER D. BAKER, M.D., Professor of Pathology.

CHARLES E. BUTTERWORTH, JR., M.D., Resident in Hematology, Jefferson-Hillman Hospital.

ARTHUR CHENOWETH, M.D., Assistant Professor of Surgery.

JOSEPH K. CLINE, Ph.D., Professor of Cancer Research.

WALTER B. FROMMEYER, JR., M.D., Instructor in Medicine (Hematology).

JAMES B. McLESTER, M.D., F.A.C.P., Associate Professor of Medicine and Executive Officer of the Department.

WILLIAM H. RISER, JR., M.D., Associate Professor of Medicine.  
 G. HARMON STOKES, M.D., Former Resident in Hematology, Jefferson-Hillman Hospital.

### *Visiting Faculty*

GOULD A. ANDREWS, M.D., Chief of Hematology, Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn.  
 W. R. ARROWSMITH, M.D., Instructor in Medicine, Tulane University of Louisiana School of Medicine, New Orleans, La.  
 IVAN W. BROWN, JR., M.D., Instructor in Surgery, Duke University School of Medicine, Durham, N. C.  
 MARSHALL BRUCER, M.D., Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tenn.  
 W. J. DARBY, M.D., Professor of Biochemistry and Assistant Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.  
 L. W. DIGGS, M.D., Professor of Medicine, University of Tennessee College of Medicine, Memphis, Tenn.  
 CHARLES M. HUGULEY, JR., M.D., Instructor in Medicine, Emory University School of Medicine, Emory University, Ga.  
 EDGAR JONES, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.  
 R. WAYNE RUNDLES, M.D., Associate in Medicine, Duke University School of Medicine, Durham, N. C.  
 HOWARD E. SKIPPER, Ph.D., Associate Director and Director of the Division of Biochemistry, Southern Research Institute, Birmingham, Ala.

This is a new course on the College schedule. It is especially scheduled to meet a demand to furnish advanced instruction in the field of Hematology to physicians in the Southeastern part of the country. Outstanding authorities are being invited from the University of Tennessee, Emory University, Vanderbilt University, Duke University, Tulane University of Louisiana and the Oak Ridge Institute of Nuclear Studies to join the faculty. Advanced instruction will be offered in the form of lectures, case reports and staff conferences in the mornings and laboratory studies in the afternoons.

The last day of the course, Saturday, December 10, will be devoted to the Southeastern Regional Meeting of The American College of Physicians comprising Alabama, Florida, Georgia, South Carolina and Cuba. Every registrant is urged to remain for the Regional Meeting. Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, is the General Chairman and Dr. Edgar G. Givhan, Jr., F.A.C.P., is Chairman of the Committee on Arrangements. The Regional Meeting program will be printed as a separate folder and will be supplied in advance to everyone in the course.

*Hotel Accommodations:* Tutwiler Hotel. Rates: Single rooms, \$3.50 to \$6.50; double rooms, \$5.50 to \$8.50; twin-bedded rooms, \$6.00 to \$8.50. Make reservations through Dr. D. O. Wright, 2930 North 16th St., P. O. Box 2603, Birmingham, Ala.

### OUTLINE OF COURSE

*Tuesday, December 6*

#### THE ANEMIAS

##### A.M. Session

8:30 Registration, Assembly and Announcements.  
 9:00-9:30 Diagnosis and Treatment of Pernicious Anemia.  
           DR. JONES.  
 9:30-10:00 Diagnosis and Treatment of Nutritional Anemias.  
           DR. DARBY.



- 10:00-10:30 Problems of Iron Metabolism.  
DR. ARROWSMITH.
- 10:30-11:00 Diagnosis and Treatment of Hemolytic Anemias.  
DR. HUGULEY.
- 11:00-11:30 Sickle Cell Anemia.  
DR. DIGGS.
- 11:30-12:00 Evaluation of Hematopoietic Agents.  
DR. JONES.
- 12:00-12:30 Megaloblastic Anemias from Gastrointestinal Diseases.  
DR. DARBY.
- 12:30- 1:00 Diagnosis and Treatment of Hypochromic Anemias.  
DR. ARROWSMITH.

## P.M. Session

- 2:00- 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

*Wednesday, December 7*

## THE LYMPHOMAS

## A.M. Session

- 9:00- 9:30 A Fundamental Search for Antileukemic Agents.  
DR. SKIPPER.
- 9:30-10:00 Treatment of Chronic Leukemia.  
DR. RISER.
- 10:00-10:30 Use of Folic Acid Antagonists in the Treatment of Acute Leukemia.  
DR. KRACKE.
- 10:30-11:00 Treatment of Multiple Myeloma.  
DR. RUNDLES.
- 11:00-11:30 Use of Hematology in Radiophysiology.  
DR. BRUCER.
- 11:30-12:00 Radio-active Isotopes in the Treatment of Leukemia.  
DR. ANDREWS.
- 12:00-12:30 Metastatic Tumors in Bone Marrow.  
DR. RUNDLES.
- 12:30- 1:00 Treatment of Hodgkin's Disease.  
DR. HUGULEY.

## P.M. Session

- 2:00- 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

*Thursday, December 8*

## HEMORRHAGIC DISEASES

## A.M. Session

- 9:00- 9:30 Modern Concepts on Coagulation of the Blood.  
DR. FROMMEYER.
- 9:30-10:00 Diagnosis of Hemorrhagic Diseases.  
DR. DIGGS.
- 10:00-10:30 Hereditary Hemorrhagic Telangiectasis.  
DR. STOKES.

- 10:30-11:00 Treatment of Hemorrhagic Diseases.  
DR. DIGGS.
- 11:00-11:30 The Problem of Hypersplenism.  
DR. KRACKE.
- 11:30-12:00 Surgical Aspects of Portal Hypertension.  
DR. CHENOWETH.
- 12:00- 1:00 Clinico-pathological Conference.  
DRS. JONES and BAKER.

## P.M. Session

- 2:00- 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

*Friday, December 9*

## MISCELLANEOUS

## A.M. Session

- 9:00- 9:30 The Inheritance of Blood Diseases.  
DR. BUTTERWORTH.
- 9:30-10:00 Biopsy of the Liver.  
DR. RUNDLES.
- 10:00-10:30 Recent Advances in Transfusion Therapy.  
DR. BROWN.
- 10:30-11:00 Evaluation of Bone Marrow Patterns.  
DR. RISER.
- 11:00-11:30 The Inheritance of Red Cell Agglutinogens.  
DR. BUTTERWORTH.
- 11:30-12:00 Practical Aspects of the Rh Problem.  
DR. BROWN.
- 12:00-12:30 Tests for Malignancy as Applied to Hematology.  
DR. CLINE.
- 12:30- 1:00 Primary and Secondary Polycythemia.  
DR. RISER.

## P.M. Session

- 2:00- 4:00 Laboratories on Sixth Floor of Jefferson Hospital for microscopic work, lantern slide demonstrations, and examination of patients by Officers of Instruction and Visiting Faculty.

*Note:* Discussions of all morning papers will take place during the Afternoon Sessions.

*Saturday, December 10*

## SOUTHEASTERN REGIONAL MEETING OF THE AMERICAN COLLEGE OF PHYSICIANS

The Annual Regional Meeting of the Southeastern States and Cuba will be held at Birmingham and the program is offered as an integral part of this postgraduate course.

# COURSE NO. 8—THE PHYSIOLOGIC APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES

(December 5-10, 1949)

THE UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE  
1200 N. STATE ST., LOS ANGELES, CALIF.

GEORGE C. GRIFFITH, M.D., F.A.C.P., *Director*

(Minimal Registration, 50;  
Maximal Registration, 125)

Fees: A.C.P. Members, \$30.00  
V. A. (P. L. 346), \$30.00  
Non-members, \$60.00

## *Consulting Committee*

PHOEBUS BERMAN, M.D.  
LEWIS T. BULLOCK, M.D.  
JAMES F. CHURCHILL, M.D., F.A.C.P.  
LELAND P. HAWKINS, M.D., F.A.C.P.  
B. O. RAULSTON, M.D., F.A.C.P.  
EDWARD C. ROSENOW, JR., M.D., F.A.C.P.  
PAUL STARR, M.D., F.A.C.P.  
HOWARD F. WEST, M.D., F.A.C.P.

## OFFICERS OF INSTRUCTION

JOHN MARTIN ASKEY, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.  
PHOEBUS BERMAN, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine; Medical Director, Los Angeles County Hospital.  
ROBERT I. BOYD, M.D., Instructor in Medicine, University of Southern California School of Medicine.  
THOMAS H. BREM, M.D., Instructor in Medicine, University of Southern California School of Medicine.  
JAMES H. BRITTON, M.D., Instructor in Medicine, University of Southern California School of Medicine.  
LEWIS T. BULLOCK, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.  
EDWARD M. BUTT, M.D., Professor of Pathology, University of Southern California School of Medicine.  
GURTH CARPENTER, M.B., M.R.C.P., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.  
RAY A. CARTER, M.D., F.A.C.R., Professor of Radiology, University of Southern California School of Medicine.  
ROBERT CLELAND, M.D., Instructor in Pediatrics, University of Southern California School of Medicine.  
SEYMOUR L. COLE, M.D., Instructor in Medicine, University of Southern California School of Medicine.  
ELIOT CORDAY, M.D., Guest Lecturer. Institute for Medical Research, Cedars of Lebanon Hospital.  
MARVIN B. CORLETTE, M.D., F.A.C.P., Instructor in Medicine, University of Southern California School of Medicine.

- RICHARD S. COSBY, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- MARVIN DARSIE, M.D., Research Associate in Surgery, University of Southern California School of Medicine.
- SIM P. DIMITROFF, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- DOUGLAS R. DRURY, M.D., Professor of Physiology, University of Southern California School of Medicine.
- DONALD T. EDMEADES, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- HUGH A. EDMONDSON, M.D., Professor of Pathology, University of Southern California School of Medicine.
- STEPHEN R. ELEK, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- EDWARD R. EVANS, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- H. RUSSELL FISHER, M.D., F.A.C.P., Professor of Pathology, University of Southern California School of Medicine.
- HARRY GOLDBLATT, M.D., Professor of Pathology, University of Southern California School of Medicine.
- GEORGE C. GRIFFITH, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California School of Medicine.
- ERNEST M. HALL, M.D., F.A.C.P., Professor of Pathology, University of Southern California School of Medicine.
- ARTHUR M. HOFFMAN, M.D., F.A.C.P., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.
- RALPH E. HOMANN, JR., M.D., Assistant Professor of Medicine, University of Southern California School of Medicine.
- ROBERT W. HUNTINGTON, JR., M.D., Associate Professor of Pathology, University of Southern California School of Medicine.
- JOHN C. JONES, M.D., F.A.C.S., Associate Clinical Professor of Surgery, University of Southern California School of Medicine.
- JULIUS KAHN, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.
- DAVID C. LEVINSON, M.D., Research Associate, Department of Cardiology, University of Southern California School of Medicine.
- MOREY L. LIPKIS, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- ALBERTO MARIANACCI, M.D., Head, Electro-encephalography Department, Los Angeles County Hospital.
- HELEN E. MARTIN, M.D., Associate Professor of Medicine, University of Southern California School of Medicine.
- LOUIS E. MARTIN, M.D., F.A.C.P., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.
- VERNE R. MASON, M.D., Clinical Professor of Medicine, University of Southern California School of Medicine.
- EDGAR F. MAUER, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- PERRY J. MELNICK, M.D., F.A.C.P., Associate Professor of Pathology, University of Southern California School of Medicine.
- HAROLD MILLER, M.D., Fellow, Department of Cardiology, University of Southern California School of Medicine.
- HYMAN MILLER, M.D., Associate Clinical Professor of Medicine, University of Southern California School of Medicine.

- WILLIAM J. MITCHELL, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- FREDERICK W. S. MODERN, M.D., F.A.C.P., Associate Clinical Professor of Medicine, College of Medical Evangelists.
- FREDERICK J. MOORE, M.D., Associate Professor of Medicine (Experimental), University of Southern California School of Medicine.
- JACKSON NORWOOD, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- GRIFFITH D. PAGE, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- HAROLD E. PEARSON, M.D., Associate Professor of Bacteriology and Parasitology, University of Southern California School of Medicine.
- DONALD W. PETIT, M.D., Assistant Professor of Medicine, University of Southern California School of Medicine.
- EDWARD PHILLIPS, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- MYRON PRINZMETAL, M.D., Senior Attending Physician and Director of Beaumont Laboratories for Cardiovascular Disease, Cedars of Lebanon Hospital.
- GUY E. RADAR, M.D., Resident in Pediatrics, Los Angeles County Hospital.
- B. O. RAULSTON, M.D., F.A.C.P., Dean and Professor of Medicine, University of Southern California School of Medicine.
- EDWARD C. ROSENOW, JR., M.D., F.A.C.P., Associate Professor of Medicine and Director, Medical Extension Education, University of Southern California School of Medicine.
- JOHN P. SAMPSON, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- JOSEPH M. SHACHTMAN, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- EDWARD SHAPIRO, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.
- JACK A. SHEINKOPF, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- PAUL STARR, M.D., F.A.C.P., Professor of Medicine, University of Southern California School of Medicine.
- CLINTON H. THIENES, M.D., Professor of Pharmacology and Toxicology, University of Southern California School of Medicine.
- WILLIAM PAUL THOMPSON, M.D., Associate Professor of Medicine, College of Medical Evangelists.
- MEYER C. THORNER, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- RICHARD F. WEBB, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- SIDNEY WEISMAN, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- HOWARD F. WEST, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California School of Medicine.
- TRAVIS W. WINSOR, M.D., F.A.C.P., Instructor in Medicine, University of Southern California School of Medicine.
- ANTON S. YUSKIS, M.D., Instructor in Medicine, University of Southern California School of Medicine.
- WILLARD J. ZINN, M.D., Fellow, Department of Cardiology, University of Southern California School of Medicine.

The physiologic approach to the clinical problems in cardiovascular disease will be the basis of the week's study. Individual symptoms, physical signs and diagnostic

technics will be discussed from the physiologic and clinical standpoints. Roentgenology, electrocardiography and cardiac catheterization will be presented from the primary viewpoint of the underlying altered physiology.

Five clinical pathological conferences will emphasize the differential diagnosis of heart disease. There will be five clinical sessions in which cases illustrating physiologic problems such as dyspnea, cyanosis, pain, edema and heart failure will be studied.

The technic and value of cardiac catheterization, anticoagulants, and newer therapeutic trends will be fully covered.

*Hotel Accommodations:* The Biltmore Hotel, Mr. Francis Bustillo, Convention Manager, Los Angeles 13, Calif. Rates: Single rooms, \$7.00-\$8.00 daily; double or twin-bedded rooms, \$13.50 daily.

Alexandria Hotel, Mr. Frank Walker, General Manager, 5th and Spring Sts., Los Angeles 13, Calif. Rates: Single rooms with bath, \$5.00-\$6.00 daily; double rooms with bath, \$7.50 daily; twin-bedded rooms with bath, \$8.50 daily.

The above hotels are located near one another and are equally convenient to the meeting place of the course. In making reservations, identify yourself with The American College of Physicians and this particular course.

#### OUTLINE OF COURSE

*Monday, December 5*

##### A.M. Session

9:00- 9:15 Registration.

9:15- 9:30 Orientation.

B. O. RAULSTON, M.D., Dean, School of Medicine.

PHOEBUS BERMAN, M.D., Medical Director, Los Angeles County Hospital.

9:30- 9:50 Physiology of Dyspnea.

Dr. HOMANN.

9:50-10:05 Clinical Aspects of Dyspnea.

Dr. NORWOOD.

10:05-10:20 The Mechanism and Radiation of Coronary Artery Pain.

Dr. GRIFFITH.

10:20-10:40 Differential Diagnosis of Chest Pain.

Dr. COSBY.

10:40-11:00 The Physiologic Basis of Drugs Used in Coronary Pain.

Dr. ELEK.

11:00-11:20 The Prevention and Rehabilitation of Coronary Thrombosis.

Dr. KAHN.

11:20-12:00 New Instrumentation in Cardiovascular Physiology.

Dr. DRURY.

##### P.M. Session

1:00- 2:00 Clinical Pathological Conference.

DRS. EDMONDSON and MASON.

2:00- 3:00 Pain Clinic.

Case—Parietal Pain.

Dr. GRIFFITH.

Case—Coronary Insufficiency.

Dr. ROSENOW.

Case—Acute Myocardial Infarction.

Dr. SHEINKOPF.

Case—Dissecting Aneurysm of the Aorta.

Dr. EDMEADES.

- 3:00- 3:20 Differential Diagnosis and Treatment of Cardiac and Bronchial Asthma.  
DR. HYMAN MILLER.
- 3:20- 4:00 Metabolism of Heart Muscle and the Effects of Drugs on Same.  
DR. THIENES.

*Tuesday, December 6*

A.M. Session

- 9:00- 9:30 Physiology of Congestive Heart Failure.  
DR. HOMANN.
- 9:30-10:05 Treatment of Congestive Failure.  
DR. CORLETTE.
- 10:05-10:20 Physiology of Cyanosis.  
DR. COSBY.
- 10:20-10:40 Differential Diagnosis of Polycythemias.  
DR. CARPENTER.
- 10:40-11:00 Effects of Anemia and Polycythemia on the Cardiovascular System.  
DR. EVANS.
- 11:00-11:20 The Significance of Clubbed Fingers.  
DR. MAUER.
- 11:20-11:40 The Mechanism of Cardiac Murmurs in Anemia.  
DR. SHAPIRO.
- 11:40-12:00 Phonocardiography in Heart Disease.  
DR. SCHACHTMAN.

P.M. Session

- 1:00- 2:00 Clinical Pathological Conference.  
DRS. HALL and HOFFMAN.
- 2:00- 3:00 Heart Failure Clinic.  
Case—Pure Left Heart Failure.  
DR. PHILLIPS.  
Case—Primary Right Heart Failure.  
DR. DIMITROFF.  
Case—Congestive Failure.  
DR. WEBB.  
Case—Constrictive Pericarditis with Edema.  
DR. LEVINSON.
- 3:00-3:20 Low Sodium Intake.  
DR. COLE.
- 3:20- 3:40 Pharmacology of Digitalis and Choice of Preparation.  
DR. SHEINKOPF.
- 3:40- 3:50 Digitalis Intoxication.  
DR. BRITTON.
- 3:50- 4:00 Cerebral Manifestations of Digitalis.  
DRS. HAROLD MILLER and MARIANACCI.

*Wednesday, December 7*

A.M. Session

- 9:00- 9:20 History, Purpose and Technic of Cardiac Catheterization.  
DR. GRIFFITH.
- 9:20- 9:40 X-Ray in Cardiac Catheterization.  
DR. CARTER.
- 9:40-10:05 Oxygen Studies in Cardiac Catheterization.  
DR. DARSIE.

- 10:05-10:20 Acyanotic Heart Disease in Cardiac Catheterization.  
DR. LEVINSON.
- 10:20-10:40 Cyanotic Heart Disease in Cardiac Catheterization.  
DR. COSBY.
- 10:40-10:50 Electrocardiogram during Cardiac Catheterization.  
DR. ZINN.
- 10:50-11:00 Summary of Studies.  
DR. GRIFFITH.
- 11:00-12:00 Cardiac Arrhythmias.  
DRS. PRINZMETAL and CORDAY, and STAFF.

## P.M. Session

- 1:00- 2:00 Clinical Pathological Conference.  
DRS. HUNTINGTON and LOUIS E. MARTIN.
- 2:00- 3:00 Rheumatic Heart Disease.  
Case—Rheumatic Fever.  
DR. GRIFFITH.  
Case—Mitral Stenosis with Auricular Fibrillation.  
DR. ASKEY.  
Case—Aortic Insufficiency and Mitral Stenosis.  
DR. LIPKIS.
- 3:00-3:30 Etiology and Pathogenesis of Rheumatic Fever.  
DR. GRIFFITH.
- 3:30- 4:00 The Diagnosis of Rheumatic Fever.  
DR. MARTIN.

*Thursday, December 8*

## A.M. Session

- 9:00- 10:30 Humoral Mechanism of Hypertension.  
DR. GOLDBLATT.
- 10:30-10:45 Early Renal Lesions Predisposing Hypertension.  
DR. BOYD.
- 10:45-11:00 Psychic Aspects of Hypertension.  
DR. PAGE.
- 11:00-12:00 Clinical Electrocardiographic Pathologic Conference.  
DR. THOMPSON.

## P.M. Session

- 1:00- 2:00 Clinical Pathological Conference.  
DRS. FISHER and HELEN E. MARTIN.
- 2:00- 2:30 Congenital Clinic.  
Case—Patent Ductus Arteriosus.  
DR. GRIFFITH.  
Case—Coarctation of Aorta.  
DR. BREM.  
Case—I. A. Septal Defect.  
DR. COSBY.  
Case—Tetralogy of Fallot.  
DR. CLELAND.
- 2:30- 3:00 The Differential Diagnosis of Congenital Heart Disease.  
DR. MARTIN.
- 3:00- 4:00 Surgery of Congenital Heart Disease.  
DR. JONES.



*Friday, December 9*

## A.M. Session

- 9:00-10:05 The Physiologic Implications Obtained from Roentgenologic Study of the Thorax.  
DR. CARTER.
- 10:05-10:20 Rupture of the Heart in Myocardial Infarction.  
DR. ASKEY.
- 10:20-10:40 Diphtheritic Myocarditis.  
DR. MITCHELL.
- 10:40-11:00 Some Interesting Cardiac Effects of Certain Primary Extra Cardiac Disturbances.  
DR. PETIT.
- 11:00-11:20 Heavy Metal Deposition in Various Organs.  
DR. BUTT.
- 11:20-11:40 Laboratory Aspects of the Diagnosis and Treatment of Bacterial Endocarditis.  
DR. PEARSON.
- 11:40-12:00 Effects of Blood Sugar Variations on the Heart and Circulation.  
DR. WEST.

## P.M. Session

- 1:00- 2:00 Clinical Pathological Conference.  
DRS. MELNICK and BULLOCK.
- 2:00- 2:15 Orthostatic Hypotension.  
DR. YUSKIS.
- 2:15- 2:30 Treatment of Shock in Acute Myocardial Infarction.  
DR. WEISMAN.
- 2:30- 2:45 Physiologic Effects of Arteriovenous Aneurysm on the Heart.  
DR. COSBY.
- 2:45- 3:15 The Heart in Thyroid Disease.  
DR. STARR.
- 3:15- 3:30 Nutritional Heart Disease.  
DR. MODERN.
- 3:30- 4:00 Anticoagulants in Cardiovascular Disease.  
DR. GRIFFITH.

*Saturday, December 10*

## A.M. Session

- 9:00-10:05 Electrocardiograms.  
Questions and Answers.  
DR. WINSOR.
- 10:05-10:20 The Q T Interval as a Diagnostic and Treatment Aid in Acute Myocarditis.  
DR. THORNER.
- 10:20-10:40 Therapeutic Hazards in Cardiac Emergencies.  
DR. HOFFMAN.
- 10:40-11:00 Morphine in Cardiac Disease.  
DR. SAMPSON.
- 11:00-11:30 The Adrenergic and Anti-adrenergic Drugs.  
DR. THIENES.
- 11:30-12:00 Adrenal Corticotropic Hormone and Compound E in Rheumatic Disease.  
DR. MOORE.

All registrations must be entered through the central office of The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

The registration in other courses, now completed, on the Autumn program of the College was gratifying, attesting to the continued popularity of these excellent courses. The 1950 schedule is being prepared by the Advisory Committee on Postgraduate Courses and will be announced in the next issue of this journal.

### REGIONAL MEETINGS

#### Reports on Recent Meetings

*Eastern Canada and New England*—Montreal, September 23-24, 1949. This was a two-day Regional Meeting covering the New England States, the Maritime Provinces and the Province of Quebec. Dr. Arthur T. Henderson, F.A.C.P., Governor for Quebec, was General Chairman; Dr. E. H. Mason, F.A.C.P. was Chairman of the Committee on Arrangements, and Dr. J. S. L. Browne, F.A.C.P. was Chairman of the Program Committee. Governors of the participating New England States and the Maritime Provinces coöperated and an attempt was made to have speakers from each State or Province. The various Governors presided over different portions of the program. All meetings were held at the Windsor Hotel, but the last afternoon was given over to visits to the Institute of Experimental Medicine and Surgery at the University of Montreal, to the Osler Library of McGill University and to the Montreal General Hospital Institute for Special Research and Cell Metabolism. The program was as follows:

#### FRIDAY MORNING SESSION

##### *Presiding Officer*

CHESTER S. KEEFER, M.D., F.A.C.P.

##### *Governor for Massachusetts*

#### 9:30-10:30 Adaptation Syndrome.

HANS SELYE, M.D., Ph.D. (by invitation), Director, Institute of Experimental Medicine and Surgery, Université de Montreal, and J. S. L. BROWNE, M.D., F.A.C.P., Professor of Medicine, McGill University, Montreal, P. Q.

#### 10:30-11:00 Coronary Sclerosis and Pulmonary Hypertension.

EUGENE H. DRAKE, M.D., F.A.C.P., Portland, Maine.

#### 11:00-11:30 Recent Developments in the Pathogenesis of Diabetes Mellitus.

MARTIN M. HOFFMAN, M.D., Ph.D. (by invitation), Assistant Professor of Medicine, McGill University, Montreal, P. Q.

#### 11:30-12:00 Shunting of Cerebrospinal Fluid into Peritoneal Cavity.

W. V. CONE, M.D. (by invitation), Associate Professor of Neurosurgery, McGill University,

REVIS LEWIS, M.D. (by invitation), and

IRA JACKSON, M.D. (by invitation); Montreal, P. Q.

#### AFTERNOON SESSION

##### *Presiding Officer*

HERMAN A. LAWSON, M.D., F.A.C.P.

##### *Governor for Rhode Island*

#### 2:00-2:30 The Use of Radioactive Isotopes in Medical Investigation and Treatment.

JOSEPH P. ROSS (by invitation), Boston, Mass.

- 2:30- 3:00 The Function and Value of Hospital Diet Committees.  
E. H. BENSLEY, M.D. (by invitation), Director of the Department of Metabolism and Toxicology, Montreal General Hospital, Montreal, P. Q.
- 3:00- 3:30 The Metabolism of Thiocyanates after Prolonged Administration in Man.  
F. C. MOISTER, M.D. (by invitation), and  
EDWARD D. FREIS, M.D. (by invitation); Hanover, N. H.
- 3:30- 3:45 INTERMISSION.
- 3:45- 4:15 Recent Advances in Neurology.  
FRANCIS McNAUGHTON, M.D. (by invitation), Associate Professor of Neurology, McGill University, Montreal, P. Q.
- 4:15- 4:45 Tension and Health.  
D. EWEN CAMERON, M.D. (by invitation), Director, Allan Memorial Institute, and Professor of Psychiatry, McGill University, Montreal, P. Q.

## EVENING

- 6:30 Cocktails.
- 7:15 Dinner (Informal).  
Toastmaster: CHARLES F. MOFFATT, M.D., F.A.C.P., Regent, American College of Physicians, Montreal, P. Q.  
Addresses: REGINALD FITZ, M.D., F.A.C.P., President, American College of Physicians, Boston, Mass.  
E. R. LOVELAND, Executive Secretary, American College of Physicians, Philadelphia, Pa.

## SATURDAY MORNING SESSION

*Presiding Officer*

HARRY T. FRENCH, M.D., F.A.C.P.

*Governor for New Hampshire*

- 9:00-10:00 PANEL DISCUSSION: Chronic Pulmonary Disease.  
J. C. MEAKINS, M.D., M.A.C.P., Chairman.  
G. W. WRIGHT, M.D. (by invitation), Trudeau Sanatorium, Saranac Lake, N. Y.  
N. D'ESOP, M.D. (by invitation), Veterans Administration Hospital, Sunmount, N. Y.  
HUGH BURKE, M.D. (by invitation), Royal Edward Laurentian Hospital, Montreal, P. Q.  
C. A. McINTOSH, M.D. (by invitation), Royal Victoria Hospital, Montreal, P. Q.  
HUGH STARKEY, M.D. (by invitation), In charge of Veteran Affairs, Queen Mary Hospital, Montreal, P. Q.
- 10:00-10:30 *B. Coli* Ulcerative Endocarditis.  
L. C. STEEVES, M.D. (by invitation), Halifax, N. S.
- 10:30-11:00 Thyrotoxicosis: Newer Aspects.  
E. B. ASTWOOD, M.D., F.A.C.P., Research Professor of Medicine, Tufts College Medical School, Boston, Mass.
- 11:00-11:15 INTERMISSION.

- 11:15-11:45 Results of the Treatment of Hypertensive Vascular Disease by Sodium Restriction.  
MICHAEL DiMAIO, M.D. (by invitation), Providence, R. I.
- 11:45-12:15 Rickettsial Pox.  
JOHN F. DALY, M.D. (by invitation), Assistant Professor of Dermatology, University of Vermont, Burlington, Vt.

---

Papers, 20 minutes; 10 minutes for discussion.

---

*Western New York*—Buffalo, October 1, 1949. The Western New York Regional Meeting has been established over many years, and has grown to be a popular and exceedingly well-attended meeting. Enthusiasm is always high and attendance is exceptionally good. The meeting was held under the Governorship of Dr. Edward C. Reifenstein, F.A.C.P., Syracuse. Dr. Edward F. Driscoll, F.A.C.P., Buffalo, was Chairman of the Committee on Arrangements and Dr. Roy L. Scott, F.A.C.P., Buffalo, was Chairman of the Scientific Program Committee. All sessions were held at the Hotel Statler. 118 members and 73 guests were registered. The program was as follows:

#### MORNING SESSION

NELSON G. RUSSELL, SR., M.D., F.A.C.P.,

Buffalo, N. Y.

*Presiding*

9:30 Liver Biopsy.

DRS. A. H. AARON, F.A.C.P., KORDEL TERPLAN, S. SANES, W. F. LIPP, W. H. CHAPPLE, A. R. LENZNER, and R. C. BAHN; Buffalo, N. Y.

9:50 The Use of Tetraethylthiuramdisulphide (Antabuse) in the Rehabilitation of the Alcoholic.

DRS. KENNETH GOLDSTEIN (Associate), L. OSBORNE, R. KIDDER, W. CORCORAN, and R. HUBBARD; Buffalo, N. Y.

10:10 Some Aspects of the Epidemiologic Problems of Rocky Mountain Spotted Fever on Long Island.

DR. JOHN K. MILLER (Associate), Albany, N. Y.

10:30 Coarctation of the Aorta.

DRS. NELSON G. RUSSELL, JR., F.A.C.P., and JOHN R. PAINE (by invitation); Buffalo, N. Y.

10:50 INTERMISSION.

RICHARD N. DENIORD, M.D., F.A.C.P.,

Buffalo, N. Y.

*Presiding*

11:00 Advances in Electrocardiography.

DR. GEORGE H. REIFENSTEIN (Associate), Syracuse, N. Y.

11:20 The Vascular Menace in Diabetes.

DR. CHARLES B. F. GIBBS, F.A.C.P., Rochester, N. Y.

11:40 Discussion by DR. REGINALD FITZ, Boston, Mass.

12:00 INTERMISSION.

12:30 LUNCHEON (Terrace Room).

## AFTERNOON SESSION

MAYNARD E. HOLMES, M.D., F.A.C.P.,

Syracuse, N. Y.

*Presiding*

- 2:20 Results of Treatment of Minimal Active Tuberculosis with Modified Bed Rest.  
DR. ROGER S. MITCHELL, JR., F.A.C.P., Trudeau, N. Y.
- 2:40 The Prevention of Diabetes.  
DR. BERNARD A. WATSON, F.A.C.P., Clifton Springs, N. Y.
- 3:00 The Rôle of the Internist in Rehabilitation.  
DR. JOHN M. NICKLAS, F.A.C.P., Saranac Lake, N. Y.
- 3:20 Production of Artificial Jaundice in the Investigation of Rheumatoid Arthritis.  
DRS. B. M. NORCROSS (Associate), L. M. LOCKIE, SR., F.A.C.P., and J. H. TALBOTT, F.A.C.P., Buffalo, N. Y.
- 3:40 The Effects of Respiration on the Circulation in Relation to Angina Pectoris and Circulatory Failure.  
DR. WILLIAM S. MCCANN, F.A.C.P., Rochester, N. Y.
- 4:00 INTERMISSION.

DR. PAUL C. CLARK, F.A.C.P., Syracuse, N. Y.

*Presiding*

- 4:10 Demonstration of Diagnostic Cells in Disseminated Lupus Erythematosus.  
DR. S. L. VAUGHAN, F.A.C.P., Buffalo, N. Y.
- 4:20 Familial Incidence of Disseminated Lupus Erythematosus.  
DR. WILLARD H. WILLIS, F.A.C.P., Utica, N. Y.
- 4:30 Idiopathic Pulmonary Fibrosis; Case Report.  
DR. R. E. SMITH (Associate), Clifton Springs, N. Y.
- 4:40 CLINICAL PATHOLOGICAL CONFERENCE.  
DR. KORNEL TERPLAN, Pathologist, Buffalo, N. Y. (by invitation).  
Discusser: DR. W. WALTER STREET, F.A.C.P., Syracuse, N. Y.

A reception and banquet were held in the evening with Dr. A. H. AARON, F.A.C.P. as Toastmaster and with the following distinguished guests:

- DR. REGINALD FITZ, F.A.C.P., Boston, Mass., President, The American College of Physicians.
- DR. WILLIAM S. MCCANN, F.A.C.P., Rochester, N. Y., Regent, The American College of Physicians.
- MR. EDWARD R. LOVELAND, Philadelphia, Pa., Executive Secretary, The American College of Physicians.
- DR. NELSON G. RUSSELL, SR., F.A.C.P., Former Governor for Western New York.
- DR. HERBERT K. DETWEILER, F.A.C.P., Toronto, Ont., Governor for the Province of Ontario.
- DR. RAY F. FARQUHARSON, F.A.C.P., Professor of Medicine, University of Toronto Faculty of Medicine.
- DR. EDWARD C. REIFENSTEIN, F.A.C.P., Syracuse, N. Y., Governor for Western New York.

---

*Mississippi*—Jackson, October 8, 1949. This regional meeting was held under the Governorship of Dr. John G. Archer, F.A.C.P., Greenville, with Dr. Gayden

Ward, F.A.C.P., acting as Chairman of the Entertainment Committee. The College membership in Mississippi is comparatively small but it is customary for every member to turn out for the annual Regional Meeting there. Their program was as follows:

*Presiding*

JOHN G. ARCHER, B.S., M.D., F.A.C.P.

Greenville, Mississippi

*Governor for Mississippi*

The Internist's Responsibility for the Elderly Surgical Patient.

W. K. PURKS, M.D., F.A.C.P., Vicksburg, Mississippi.

Coarctation of Aorta With Report of Two Cases Operated upon Successfully.

GAYDEN WARD, M.D., F.A.C.P.

GEORGE HARVEY, JR., M.D. (by invitation), Jackson, Mississippi.

Prognosis of Heart Disease.

BEN R. HENINGER, M.D., F.A.C.P., Gulfport, Mississippi.

Management of Congestive Heart Failure.

SAMUEL NADLER, M.D., F.A.C.P., Associate Professor of Clinical Medicine, Tulane University, New Orleans, Louisiana.

Psychosomatic Medicine.

JAMES F. LEWIS, M.D., F.A.C.P., Columbus, Mississippi.

Amyloid Disease.

DOUGLAS D. BAUGH, M.D., F.A.C.P., Columbus, Mississippi.

Lower Nephron Nephrosis. (*Acute Renal Failure.*)

WESLEY W. LAKE, M.D., F.A.C.P., Pass Christian, Mississippi.

The Problem of Hypersplenism.

ROY KRACKE, M.D. (by invitation), Dean, Medical College of Alabama, Birmingham, Alabama.

SOCIAL HOUR.

BANQUET (INFORMAL).

Toastmaster—MR. GEORGE GODWIN, Jackson, Mississippi.

Speaker—GOV. FIELDING WRIGHT, Governor of Mississippi.

*Puerto Rico*—Santurce, October 16, 1949. This was the first Regional Meeting ever formally organized in Puerto Rico. Dr. Rafael Rodriguez-Molina, F.A.C.P., as the Governor for the Island, organized the meeting and former President, Hugh J. Morgan, F.A.C.P., was the special representative from the Board of Regents. The program was as follows:

PROGRAM

*Presiding Officer*

RAMON M. SUAREZ, M.D., F.A.C.P., San Juan

Bleeding Tendency Due to Circulating Anticoagulants, with Report of a Case.

EDUARDO R. PONS, JR., M.D. (by invitation), and MERCEDES VICENTE DE TORREGROSA, Ph.D. (by invitation), San Juan City Hospital.

Pathogenesis of Schistosomiasis with Special Reference to Schistosomal Cirrhosis.

ENRIQUE KOPPISCH, M.D., F.A.C.P., Acting Director and Professor of Pathology, School of Tropical Medicine, San Juan.

The Present Status of the Intradermal Reaction in the Diagnosis of Schistosomiasis and Filariasis.

JOSE OLIVER-GONZALEZ, Ph.D. (by invitation), Associate Professor of Medical Zoölogy, School of Tropical Medicine, San Juan.

Myocarditis.

HUGH J. MORGAN, M.D., D.Sc., F.A.C.P., Regent and Former President, The American College of Physicians; Professor of Medicine, Vanderbilt University School of Medicine; Physician-in-Chief, Vanderbilt University Hospital; Nashville, Tenn.

Incidence of Hypertension in Puerto Rico.

RAMON M. SUAREZ, M.D., F.A.C.P., Director, Mimiya Hospital; Consultant in Medicine, Veterans Administration Center, San Patricio Hospital; San Juan.

Electrocardiographic Changes in Phosphorus Poisoning.

RURICO S. DIAZ-RIVERA, M.D., F.A.C.P., Chief, Medical Service, San Juan City Hospital.

Treatment of Amebiasis with A.D. 4712.

FEDERICO HERNANDEZ-MORALES, M.D., F.A.C.P., Associate Professor of Tropical Medicine, School of Tropical Medicine, and ENRIQUE PEREZ-SANTIAGO, M.D. (by invitation), Medical Supervisor, University Hospital, San Juan.

Meningitis in Infants and Children in Puerto Rico.

ANTONIO ORTIZ-ORTIZ, M.D., F.A.C.P., Chief, Pediatric Service, San Juan City Hospital.

Hypercholesteremia and Its Relation to Coronary Artery Disease.

ROBERTO FRANCISCO AZIZE, M.D., F.A.C.P., Director, San Juan Diagnostic Clinic.

#### EVENING

#### CONDADO BEACH HOTEL

8:30 Dinner (Formal).

#### *Presiding Officer*

RAFAEL RODRIGUEZ-MOLINA, M.D., F.A.C.P.

Governor of The American College of Physicians; Chief, Medical Service, San Patricio Hospital, Veterans Administration Center; Assistant Professor of Tropical Medicine, School of Tropical Medicine; San Juan, P. R.

#### ADDRESS

DR. HUGH J. MORGAN, Nashville, Tenn.

Regent and Former President of The American College of Physicians

---

*Arizona*—Phoenix, October 22, 1949. Dr. Leslie R. Kober, F.A.C.P., as Governor for Arizona, organized and directed the meeting. Dr. Joseph Bank, F.A.C.P., and Dr. Hilton J. McKeown, F.A.C.P., both of Phoenix, were Chairmen of the Program Committee and the Arrangements Committee, respectively. This was the first Arizona Regional Meeting of the College. The Arizona membership numbers but 43, but the great majority were in attendance and brought with them a number of guests who were interested in the College and the program. It is anticipated that the success of this meeting will result in annual clinical programs of increasing value and importance to the medical profession in Arizona. Their program was as follows:

## PROGRAM

Panel Discussion: Climatic Influence on Disease.

Climate and Respiratory Diseases.

KENT H. THAYER, M.D., F.A.C.P., Phoenix.

Climate and Metabolic Disturbances.

LESLIE B. SMITH, M.D., F.A.C.P., Phoenix.

Climate and Rheumatic Diseases.

HARRY E. THOMPSON, M.D., F.A.C.P., Tucson.

Discussion.

Early Diagnosis of Cor Pulmonale.

GEORGE C. GRIFFITH, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California, Los Angeles, California.

Biochemical Studies in Demyelinating Disease.

HAROLD H. JONES, M.D., F.A.C.P., Regent and Former Governor for Kansas of The American College of Physicians, Winfield, Kansas.

Recent Advances in The Treatment of Arthritis.

W. PAUL HOLBROOK, M.D., F.A.C.P., President, The Arthritis and Rheumatism Foundation, and DONALD F. HILL, M.D., F.A.C.P., Tucson.

Lower Abdominal Aneurysms.

LOUIS B. BALDWIN, M.D., F.A.C.P., Phoenix.

Non-tuberculous Intra-thoracic Lesions.

HAROLD KOHL, SR., M.D. (Associate), Tucson.

Necrotizing Arteritis Resulting from Generalized Fungus Infection.

ONIE O. WILLIAMS, M.D. (Associate), Director of the Clinical Laboratory and Pathologist, St. Joseph's Hospital, Phoenix.

Indications for Thoracotomy.

HOWELL S. RANDOLPH, M.D., F.A.C.P., Phoenix.

## EVENING

RECEPTION AND COCKTAILS.

DINNER (INFORMAL).

Toastmaster: ROBERT S. FLINN, M.D., F.A.C.P., Phoenix, President, Arizona State Medical Association.

Distinguished Guest Speakers:

HAROLD H. JONES, M.D., F.A.C.P., Regent, Winfield, Kansas. "The American College of Physicians—Present Trends."

GEORGE C. GRIFFITH, M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California, Los Angeles, California. "Physiological Findings in Arteriovenous Aneurysms by Cardiac Catheterization Methods."

---

*Midwest Regional Meeting*—Indianapolis, November 19, 1949. Dr. J. O. Ritchey, F.A.C.P., Governor for Indiana, General Chairman, with the coöperation of the College Governors for Illinois, Iowa, Michigan, Minnesota, Ohio and Wisconsin. Dr. William S. Middleton, F.A.C.P., Madison, Wis., President-Elect, A.C.P., was the chief speaker at the banquet. Copy of the program is not available at the time this copy goes to press.

---

*New Jersey Regional Meeting*—Newark, November 30, 1949. Dr. George H. Lathrope, F.A.C.P., Governor for New Jersey, General Chairman; Dr. Johannes F. Pessel, F.A.C.P., Trenton, Chairman of the Program Committee; Dr. Jerome G. Kauf-



man, F.A.C.P., Newark, Chairman of Arrangements. A copy of this program is not available at the time this goes to press. However, Dr. Edward A. Strecker, F.A.C.P., Philadelphia, will be a special guest speaker on the scientific program; and Dr. Reginald Fitz, F.A.C.P., Boston, President of the College; Dr. George Morris Piersol, M.A.C.P., Philadelphia, Secretary-General; Dr. William D. Stroud, F.A.C.P., Philadelphia, Treasurer; Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Regent; Dr. Thomas M. McMillan, F.A.C.P., Governor for Eastern Pennsylvania; and Mr. E. R. Loveland, Executive Secretary, are among the guests.

---

*Kentucky Regional Meeting*—Louisville, December 3, 1949. Dr. J. Murray Kinsman, F.A.C.P., Governor. Dr. William S. Middleton, F.A.C.P., President-Elect, American College of Physicians, special guest speaker. Other details of the program will be published later.

---

*North Carolina Regional Meeting*—Winston-Salem, December 9, 1949. Dr. Paul F. Whitaker, F.A.C.P., Kinston, Governor for North Carolina; Dr. Edward S. Orgain, F.A.C.P., Durham, Chairman of the Program Committee. Meetings will be held in the amphitheatre of the Bowman Gray School of Medicine starting at 2 p. m. Copy of the program not available when this copy goes to press.

---

*Southeastern Regional Meeting*—Birmingham, Ala., December 10, 1949. Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, General Chairman; Dr. Edgar G. Givhan, Jr., F.A.C.P., Chairman of Arrangements Committee. This Regional Meeting covers Alabama, Florida, Georgia, South Carolina and Cuba, and marks the first occasion at which this meeting has been held in Alabama. Dr. Reginald Fitz, F.A.C.P., Boston, President of the College, will be the special guest speaker at the banquet. Other details of the program yet to be published and sent to all members in the territory.

---

*Eastern Pennsylvania Regional Meeting*—Philadelphia, January 20, 1950. Dr. Thomas M. McMillan, F.A.C.P., Governor for Eastern Pennsylvania, General Chairman. Meeting will be initiated by a buffet luncheon at the Headquarters of the College, followed by a scientific program and a reception and dinner at the Warwick Hotel. Program will be printed later and distributed to all in the territory.

---

*Kansas Regional Meeting*—Topeka, March 17, 1950. Dr. William C. Menninger, F.A.C.P., Governor and General Chairman. Dr. Hugh J. Morgan, F.A.C.P., Regent of the College, Nashville, Tenn., special guest speaker. Program to be published and sent to all members in the territory.

---

The Fifteenth Annual Meeting of the Postgraduate Medical Assembly of South Texas will be held at Houston, November 29 to December 1, 1949. Among the distinguished guest speakers are Dr. Louis H. Clerf, F.A.C.P., Philadelphia, Pa., Dr. Francis M. Rackemann, F.A.C.P., Boston, Mass., and Dr. Paul D. White, F.A.C.P., Boston, Mass.

---

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va., has been elected President of the new West Virginia Medical Licensing Board.

Emory University School of Medicine in coöperation with the Medical Association of Georgia offers annually a week's postgraduate course in Medicine and Surgery for general practitioners. The last such course was concluded on October 14, and was well attended by practitioners, particularly from the State of Georgia. The registration fee is \$10.00 for the week.

---

The New Jersey Fellows of the American Academy of Pediatrics in conjunction with the Medical Society of New Jersey and the New Jersey State Department of Health recently concluded a study of child health services in the State of New Jersey. The study covers county groups in New Jersey, ratio of children to physicians, distribution of children and physicians, general hospitals admitting children, location of general hospitals admitting children, child medical care in New Jersey on an average day, medical well-child conferences, distribution of health nurses and home visits, hospitals admitting polio patients, community mental hygiene clinics, etc. Dr. Harrold A. Murray, F.A.C.P., Newark, N. J., was the Study Director.

---

Yale University School of Medicine has initiated a series of short postgraduate courses in a coöperative program with the Connecticut State Medical Society in the Hartford Hospital. These courses are designed to give physicians an opportunity to become familiar with new knowledge, procedures, and point of view, and to assist them in practicing better medicine. Courses cover various fields of medicine and surgery.

---

#### ANNOUNCEMENT OF VAN METER PRIZE AWARD

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Houston, Texas, March 9 to 11, 1950.

The competing essays may cover either clinical or research investigations; may not exceed three thousand words in length, must be presented in English; and a typewritten, double spaced copy, in duplicate, sent to the Corresponding Secretary, Dr. George C. Shivers, 100 E. St. Vrain Street, Colorado Springs, Colorado, not later than January 15, 1950.

---

"The Place of Veterans Problems in Tuberculosis Control" was the subject of an address before the Southern Tuberculosis Conference at Memphis, Tennessee, September 15, 1949, by Dr. Leo V. Schneider, F.A.C.P., Chief of the Tuberculosis Control Section of the Veterans Administration, Tuberculosis Division, Washington, D. C.

---

Dr. J. A. Rosenkrantz (Associate) was promoted to Assistant Chief of Professional Services of the Kingsbridge Veterans Administration Hospital, Bronx, New York, during September.

---

#### CIVILIAN CONSULTANTS APPOINTED TO U. S. AIR FORCE MEDICAL SERVICE

Dr. W. Paul Holbrook, F.A.C.P., Tucson, Arizona, and Dr. Phillip T. Knies, F.A.C.P., Columbus, Ohio, have been appointed Consultants in Internal Medicine to the U. S. Army Air Force Medical Service. Dr. Charles E. Kossmann, F.A.C.P., New York City, has been appointed as Civilian Consultant in Cardiology.

Dr. Lowell T. Coggeshall, F.A.C.P., resigned as Chairman of the Department of Medicine of the Division of Biological Sciences at the University of Chicago on July 1, in order to devote his full time to research and to the Deanship of the medical school. His successor is Dr. Wright R. Adams, Professor of Medicine and Associate Dean.

---

Separate surveys are being conducted by Dr. Alan Gregg, Director of Medical Science, Rockefeller Foundation, and Dr. Harman G. Weiskotten, Dean of Syracuse University College of Medicine, concerning the need for the establishment of a four-year school of medicine and dentistry in West Virginia.

---

Under the presidency of Dr. George E. Baker, F.A.C.P., Casper, the Wyoming State Medical Society held its annual meeting in Casper, September 12 to 14, 1949.

---

Dr. Howard A. Rusk, F.A.C.P., Chairman of the Department of Rehabilitation and Physical Medicine, New York University College of Medicine, has been on an extended trip to Europe to participate in teaching seminars on rehabilitation and to confer with officials of the World Health Organization in Geneva, officials of UNESCO in Paris, and to observe rehabilitation activities in England. Dr. Rusk is Consultant in Rehabilitation to the Department of Social Affairs of the United Nations.

---

#### SOUTHWESTERN MEDICAL COLLEGE TO BECOME STATE UNIVERSITY

The Board of Regents of the University of Texas has announced acceptance of the offer of the Southwestern Medical Foundation to turn over the facilities of the Southwestern Medical College. Nearly one and one-half million dollars in assets were turned over to the University of Texas, and a medical branch of the University of Texas will be established in Dallas. The new school will be known as "Southwestern Medical School."

---

#### DR. GEORGE F. LULL RECEIVES LEGION OF HONOR MEDAL

General George F. Lull, F.A.C.P., former Deputy Surgeon General of the United States Army and now General Manager and Secretary of the American Medical Association, was presented with the Legion of Honor Medal by the French Government in recognition of his activities on behalf of the French people immediately following World War II. Dr. Lull, at an earlier time, was awarded the Distinguished Service Medal in this country.

---

Dr. Milton L. Hobbs, F.A.C.P., Morgantown, West Virginia, has been elected Secretary-Treasurer of the Association of Pathologists of West Virginia.

---

Dr. Delivan A. MacGregor, F.A.C.P., Wheeling, College Governor for West Virginia, and Dr. Frank J. Holroyd, F.A.C.P., Princeton, have been appointed Chairman and Member, respectively, of a Liaison Committee between the West Virginia State Medical Association and the Board of Governors of West Virginia University. The purpose of the Committee is to establish more effective relations between the two institutions and a better understanding of the needs of the medical profession in the field of medical education.

## GEORGE MINOT LECTURESHIP

The Section on Experimental Medicine and Therapeutics of the American Medical Association recently established the George Minot Lectureship in honor of Dr. Minot's contributions to medical knowledge of the causes and methods of control of pernicious anemia. The first lecture will be arranged during 1950 or 1951. Dr. Minot (Boston) has been a Fellow of the American College of Physicians since 1928.

---

## COURSES IN POLIOMYELITIS

The University of Colorado Medical Center, aided by grants from the National Foundation for Infantile Paralysis, will give a series of postgraduate courses on Poliomyelitis, March 13-16, 1950, and May 22 to 27, 1950. The comprehensive care of patients in an epidemic will receive chief emphasis. Courses will be open to physicians west of the Mississippi River.

---

Dr. Thomas F. Walker, F.A.C.P., Great Falls, was recently installed as President of the Montana State Medical Association.

---

The Institute of Industrial Health of the University of Cincinnati conducted a course for physicians entitled "The Lead Problem in Industry," November 7 to 11, 1949. The course covered the background of the subject, of analytical and engineering considerations, inorganic lead intoxication, organic lead intoxication, economic and legal considerations. The class was limited to thirty-five physicians and the fee was \$50.00.

---

## SYMPOSIUM ON INHALATIONAL THERAPY

The Committee on Public Health Relations of the New York Academy of Medicine, in coöperation with the New York Association of Oxygen and Ambulance Services, will present a Symposium on Inhalational Therapy, consisting of exhibits, demonstrations, motion pictures, and lectures, at the Academy building, 2 E. 103rd Street, New York City, December 5 to 10, 1949. This course will bring to physicians interested in this field information about recent developments in this aspect of therapy and the efficient use of the equipment available for it.

---

Dr. J. Harry Murphy, M.D., F.A.C.P., was recently elected President of the Nebraska Tuberculosis Association.

---

A new periodical in an important field will begin publication in February 1950. It will be called "ANGIOLOGY, The Journal of Peripheral Vascular Diseases." Editor-in-Chief will be Dr. Saul S. Samuels, Chief of the Department of Peripheral Arterial Diseases, Stuyvesant Polyclinic, New York City.

Among Associate Editors in the United States are Dr. Alton Ochsner, of Tulane; Dr. Keith Grimson, of Duke; Dr. Leo Loewe, of Long Island Medical College; Dr. D. W. Kramer, of Jefferson; Dr. Gerald Pratt, of N. Y. University Medical School. A number of prominent foreign physicians will also serve. The Williams & Wilkins Company, of Baltimore, will be the publishers.

---

Dr. Joseph B. Kirsner, F.A.C.P., of the University of Chicago, has been elected President of the American Gastroscopic Society.

**"CIRCULATION," NEW OFFICIAL JOURNAL OF THE AMERICAN HEART ASSOCIATION**

A new official monthly journal of the American Heart Association, "CIRCULATION," will begin publication in January, 1950. The American Heart Association will terminate sponsorship of the monthly, "American Heart Journal," with the December, 1949 issue. This latter journal has been published heretofore for the Association by the C. V. Mosby Company.

Dr. Thomas M. McMillan, F.A.C.P., Philadelphia, continues as Editor-in-Chief for the Association.

The subscription rate will be \$12.00 (\$13.00 to foreign countries).

---

**ENLARGED MEDICAL CENTER PLANNED AT UNIVERSITY OF MICHIGAN**

According to the details of a plan announced by President Alexander G. Ruthven, the University of Michigan is planning an enlarged medical center within a few years. The cost is estimated at approximately twenty million dollars. Stimulus for the plan was based largely on the receipt of a grant of three million dollars from the Kresge Foundation of Detroit for the erection of a Medical Research Institute building, one of five new major units needed for the enlarged medical center. It is expected that the building will be started within a few months and will be erected just west of the University Hospital and attached to it. President Ruthven said that other buildings in the future plan will be an out-patient clinic, a maternity hospital, a medical and nursing education building, and a children's and infants' hospital.

The State Legislature at its last session appropriated \$100,000.00 for the drawing of plans for an outpatient clinic which, along with the research building, had been regarded as foremost among unmet needs.

The University is fully cognizant of the necessity to provide medical education for a larger number of students. Present undergraduate enrollment of the Medical School is 494 students, 151 of them in the first year class. Nearly 1500 applicants must be rejected each year recently, some of them almost as well qualified as those who are accepted, but cannot be admitted for lack of facilities and teaching and clinical staff. This year only 10 applicants from outside Michigan were admitted.

---

**UNITED STATES PUBLIC HEALTH SERVICE ANNOUNCES REGULAR CORPS EXAMINATION FOR MEDICAL OFFICERS**

A competitive examination for appointment of Medical Officers in the Regular Corps of the United States Public Health Service will be held on January 9, 10, and 11, 1950. Examinations will be held at a number of points throughout the United States, located as centrally as possible in relation to homes of candidates. Applications must be received no later than December 12, 1949.

The Regular Corps is a commissioned officer corps composed of members of various medical and scientific professions, appointed in appropriate professional categories such as medicine, dentistry, nursing, engineering, pharmacy, etc. All commissioned officers are appointed to the general service and are subject to change of station.

Appointments will be made in the grades of Assistant Surgeon (1st Lt.) and Senior Assistant Surgeon (Captain). Appointments are permanent and provide opportunities to qualified physicians for a life time career in clinical medicine, research, and public health.

Requirements for appointment in the grade of Assistant Surgeon: the applicant must be a citizen of the United States, at least 21 years of age, and a graduate from a recognized school of medicine. Physicians who are successful in the examination

and are now serving internships will not be placed on active duty in the Regular Corps until completion of internship. Applicants for appointment in the grade of Senior Assistant Surgeon must meet the above requirements and must have had a total of at least 10 years of educational training and professional experience subsequent to high school. The entrance examination will include written professional tests, an oral interview, and a physical examination.

The professional written examination for the grade of Assistant Surgeon will cover the following subjects: 1. anatomy, physiology, biochemistry; 2. materia medica and therapeutics; 3. obstetrics and gynecology; 4. practice of surgery; 5. practice of medicine; 6. epidemiology and hygiene; 7. pathology and bacteriology. Senior Assistant Surgeon applicants will be examined on subjects 4, 5, 6, and 7 listed above.

Gross pay is governed by the Career Compensation Act of 1949, and is identical to that of officers of equivalent rank in the Army and Navy. Under current law, entrance pay for an Assistant Surgeon with dependents is \$5,686.56 per annum; for Senior Assistant Surgeon with dependents, \$6,546. These figures include the \$1,200 annual additional pay received by medical officers as well as subsistence and rental allowance.

Promotions. Provisions are made for promotion at regular intervals up to and including the grade of Senior Surgeon (Lt. Col.) and for selection for promotion to the grade of Medical Director (Col.).

Retirement pay after 30 years of service or at the age of 64, is three-fourths of annual base pay at the time of retirement. Retirement for disability is authorized under the Career Compensation Act and disability retirement pay is at a minimum, one-half of the annual base pay at the time of retirement.

Additional benefits include 30 days annual leave, sick leave, full medical care, and many of the usual privileges extended to members of the military forces.

Application forms and additional information may be obtained by writing to the Surgeon General, United States Public Health Service, Federal Security Agency, Washington 25, D. C. Attention: Division of Commissioned Officers. Applications received after December 12, 1949, will not be accepted for this examination, but will be admitted to the examination in May, 1950.

## OBITUARIES

## DR. WILLIAM RAMSEY BLUE

William Ramsey Blue, M.D., F.A.C.P., died in Memphis on September 8, 1949, following a long illness.

He was born in Gallatin, Tennessee, 61 years ago and received his medical degree from Vanderbilt University in 1911. He practiced with his brother, Dr. J. B. Blue, in Parkin, Arkansas, until he came to Memphis in 1918.

Being a very good student of medicine, he felt the need of postgraduate training. In 1917 he went to New York and worked at the Nursery and Child's Hospital, preparing himself for the specialty of pediatrics. This specialty he followed until sixteen years ago when he became interested in the field of internal medicine.

His ability to teach led to his appointment as Associate Professor of Medicine at the University of Tennessee College of Medicine.

In addition to being a life member of the American College of Physicians, he was a member of the Memphis and Shelby County Medical Society, the Tennessee State Medical Association and the American Medical Association.

Dr. Blue was in every way a credit to his profession. He hewed to the line on medical ethics and had no patience with anyone who was not willing to make every sacrifice to keep the practice of medicine on a very high plane.

WILLIAM C. CHANEY, M.D., F.A.C.P.,  
Governor for Tennessee

## WILLIAM WASHINGTON GRAVES

William Washington Graves, M.D., F.A.C.P., was one of the physicians who bridged over the changes in neuropsychiatry from the last two decades of the previous and the first half of the present century. Born in 1865 in LaGrange, Kentucky, and graduated with a Doctor of Medicine degree from the St. Louis College of Physicians and Surgeons in 1888, he early turned his special attention to the study of the basic sciences of anatomy, pathology and anatomic neurology, thus laying the ground work for his future specialization. He spent almost three years in Europe, particularly in Germany and Austria, as a roaming student, visiting all the great universities and registering for special courses under the great masters, the outstanding teachers of the first decade of the present century. When he returned to St. Louis in 1905, he became instructor in the Department of Neurology in the St. Louis University School of Medicine and continued as a faculty member of that institution up to the year 1948 when he became Emeritus Professor and Director Emeritus of his department. He was appointed to the professorship in 1914 and to the directorship of the department of Neurology and Psychiatry in 1925. He served as consultant in neurology in practically all of the hospitals of St. Louis at one time or another, both in the public as well as in the private institutions.

Dr. Graves's investigations, it is interesting to note, dealt with problems that were at first sight quite remote from the area of his clinical practice. The study of the structure and the characteristics of the shoulder blade might well at first sight seem to be a purely morphological study; for Dr. Graves, however, that study was the beginning of a long pathway into the unknown which he had projected and on which he progressed during more than thirty years, not very far, it must be admitted, but sufficiently far to have his efforts achieve significance. Dr. Graves became more and more interested in the relation between physical and mental characteristics and while it must be confessed that research in that field progressed faster than Dr. Graves himself could follow, nevertheless, his own personal philosophy won for him an invitation to discuss his viewpoints before the University of Edinburgh. If Dr. Graves's

morphological studies had been conducted a generation earlier, they would, no doubt, have contributed greatly to the progress of morphological and statistical genetics. As it was, they were conducted during the time when the study of heredity was leading into physiological and biochemical interpretations. Dr. Graves sensed this and with his accustomed insistent determination, he attempted to follow. Unfortunately, his health began to fail fully fifteen years ago, forcing him to place a limit on the incredibly long hours of devotion to the study which he had determined to make his life work. His mass of data and his osteological collection represent an expenditure of energy and time equalled to the knowledge of the writer by no other investigators, even by those who gave their full time to their research.

To know and understand Dr. Graves, one must understand and know not only his scientific and his clinical work but also his human characteristics, his kindness, his broad sympathies, his desire to alleviate suffering—a desire which had been enormously stimulated by reason of his own personal sufferings, his idealism and, above all, his ability to interpret favorably to the individual almost any kind of transgression. He was one of those rare individuals who applied in his own life the full truth of the proverb, "To know all is to excuse all." By nature and by choice, innately as well as by his education and by his self-discipline, he was a gentleman. His long period of failing health and his sufferings were terminated by death on April 19, 1949.

ALPHONSE M. SCHWITALLA, S. J., Dean Emeritus,  
St. Louis University School of Medicine.

#### DR. WILHELM S. ANDERSON

Dr. Wilhelm S. Anderson, F.A.C.P., Northfield, Minnesota, died June 26, 1949, at the age of 73, of coronary thrombosis. Dr. Anderson attended St. Olaf's College, then transferred to the University of Minnesota College of Medicine and Surgery from which he received his medical degree in 1903. He spent some periods of post-graduate study at Harvard Medical School and the New York Post-Graduate Medical School and Hospital. For a number of years he practiced medicine at Grand Forks, North Dakota. In 1927, he entered the U. S. Veterans Administration and served continuously in that service until his retirement about 1946. Dr. Anderson was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1931.

#### DR. THOMAS KRAPFEL LEWIS

Thomas Krapfel Lewis, M.D., F.A.C.P., born in Merchantville, N. J., January 7, 1887, died in New Haven, Conn., August 28, 1949, of ventricular fibrillation, following an acute coronary occlusion five days previous.

His elementary education was received in the Merchantville public schools, following which he graduated from the New Jersey Friends' Academy of Moorestown, Haverford College in 1909, and the University of Pennsylvania School of Medicine in 1913. His internship was served at the Cooper Hospital, Camden, N. J., 1913-14.

As an internist he practiced in Camden, N. J., from 1914 until the time of his death, except for eighteen months while he served overseas in the First World War as Commanding Officer of the 165th Ambulance Company of the Rainbow Division.

Following his return from the army Dr. Lewis became active in civic, fraternal, and medical affairs. He was a Past President of the Camden Lions Club and a Past President of the Camden City and Camden County Medical Societies.

In 1921, he was appointed Attending Physician to the Cooper Hospital, and in 1946, he was elected Chief of the Medical Division of the Staff of this Hospital, which position he held until his death.



While Chairman of the Executive Committee of the Staff of the Cooper Hospital, he rendered a unique service by helping coördinate the interests of the Board of Managers and the Medical Staff.

Dr. Lewis was a prominent figure in the New Jersey Medical Society for many years, having served as a member of the Welfare Committee from 1933 to 1938, Chairman of the Sub-Committee on Medical Practice from 1933 to 1938, as Trustee in 1935. Some of his most valuable work was done while serving as Chairman of the Sub-Committee on Medical Practice of the State Society, in connection with the distribution of medical care. During this period he attracted wide attention by his analysis of the problem of the medical care of the indigent. Keenly interested in the Voluntary Plan movement, Dr. Lewis was a member of the various committees appointed by the State Medical Society to study the organization of a medical service plan, and he was actively associated with both the Medical Service Administration and the Medical Surgical Plan since their inception in 1938, serving as president of each organization since 1942.

Dr. Lewis served with distinction from 1942 until the time of his death as a member of the House of Delegates of the American Medical Association from New Jersey.

He was elected a Fellow of the American College of Physicians in 1939. His city and state have lost a good citizen and an outstanding physician. Those associated with him at the Cooper Hospital and in the New Jersey State Medical Society will long remember him as an untiring worker in the interests of organized medicine and the public welfare.

RALPH K. HOLLINSHED, F.A.C.P.

#### DR. G. CARROLL LOCKARD

On August 7, 1949, Dr. G. Carroll Lockard, F.A.C.P., of Baltimore, died as a result of complications following an operation.

Dr. Lockard was born in Baltimore in 1882. He attended Baltimore City College and University of Maryland, graduating in 1903.

At the time of his death, Dr. Lockard was Professor of Clinical Medicine at the University of Maryland School of Medicine and Visiting Physician at the University Hospital. He was a Diplomate of the American Board of Internal Medicine, a member of the Medical and Chirurgical Faculty of the State of Maryland, of the American Medical Association, and a Fellow of the American College of Physicians, attaining this honor in 1923.

Dr. Lockard was one of Baltimore's leading physicians, and was best known in the teaching life at the University of Maryland School of Medicine. He was honored and loved by all his students, and in his passing Baltimore has lost a very fine physician and, to those who knew him, a good friend.

WETHERBEE FORT, M.D., F.A.C.P.,  
Governor for Maryland

#### DR. CECIL McKEE JACK

Dr. Cecil M. Jack died June 28, 1949. He was born in Decatur, Ill., November 15, 1876. He received his Ph.B. in 1899 and his M.D. in 1902 from the University of Michigan. For a great many years he was connected with the Decatur and Macon County Hospital and the Decatur Contagious Hospital. He served as President of the Macon County Tuberculosis Board, Macon County Tuberculosis Sanatorium. He was a Diplomate of the American Board of Internal Medicine, a member of the National Tuberculosis Association, Illinois State Medical Society, Illinois Trudeau

Association, a former president of the Decatur Medical Society and the Illinois State Tuberculosis Association. He had been a Fellow of the American College of Physicians since 1919 and served as Governor of the College for Southern Illinois since 1941.

A number of years ago, Dr. Jack initiated legal action and won the principle that the expenses for professional travel to scientific meetings shall be deductible from income in connection with the Federal Income Tax. This has saved physicians and allied professional men literally hundreds of thousands of dollars annually.

A smiling face and a warm handshake greeted his friends and colleagues at each and every meeting of the College, regional and national. He gave his time and effort in building the American College of Physicians and aided in selecting physicians who would be a credit to our College.

Dr. Jack was an outstanding internist in his community and his opinions were built on honesty and keen clinical judgment. We shall miss him as our true friend and Governor in Southern Illinois.

GEORGE W. PARKER, M.D., F.A.C.P.

#### DR. PAUL EDWARD SIMONDS

Dr. Paul Edward Simonds, F.A.C.P., Riverside, Calif., died July 10, 1949, age 72. He was born in Detroit, Mich., October 12, 1876, pursued two years of collegiate work at Napa College and the University of Denver. He received his medical degree from the University of Southern California School of Medicine in 1908. He was a past Secretary, past Vice President and past President of the Riverside County Medical Association, past President of the Southern California Medical Association, a member of the California State Medical Association and of the American Medical Association. He had been a Fellow of the American College of Physicians since 1930, and he was a Diplomate of the American Board of Internal Medicine. His special interests were in the field of Internal Medicine and Geriatrics. In his later years, his practice was very limited. For more than twenty-five years, he had made a great contribution to the Boy Scout movement in the Riverside area. He was a family physician in the finest sense and contributed a great deal in keeping the practice of medicine in his county at a high level.

#### DR. ROBERT EDWARD WESTMORELAND, SR.

Dr. Robert Edward Westmoreland, Sr., an Associate of The American College of Physicians since 1947, aged 40, Chief of the Medical Service at the Veterans Administration Hospital in Indianapolis, died June 30, 1949, at the Mayo Clinic in Rochester, Minnesota, of cardiac failure.

Dr. Westmoreland was born at Petersburg, Virginia, July 17, 1908. He received his B.S. from the University of Virginia in 1928 and his M.D. from the University of Virginia Department of Medicine in 1932. He interned from 1932 to 1934 at the New York Postgraduate Hospital, and thereafter was Assistant Physician to the Hospital and Attending Physician to the Dispensary for some years. He served in the Medical Corps, U. S. Army from 1942 to 1946, attaining the rank of Major. Thereafter, he entered the Veterans Administration and became Chief of the Medical Service at the Indianapolis Veterans Administration Hospital. He was a member of the New York County Medical Society, the State of New York Medical Society and the American Medical Association, and a diplomate of the American Board of Internal Medicine.

## DR. JACOB JOHN WESTRA

Dr. Jacob John Westra was born March 2, 1908, in Grand Rapids, Michigan, and died in Champaign, Illinois, July 17, 1949.

Dr. Westra received his B.A. degree from Calvin College of Grand Rapids, Michigan, in 1929, and his Ph.D. degree in physiology from the University of Chicago in 1933. He then taught physiology at the University of Texas Medical School for two years, following which he returned to Chicago and entered Rush Medical College as a student where he received his M.D. degree in 1937. He served a two-year internship at the Presbyterian Hospital in Chicago from 1936 to 1938. He then entered the Mayo Clinic as a Fellow in Internal Medicine, continuing to October, 1939. From 1940-44 he was in private practice. In 1944, he joined the Staff of the Christie Clinic of Champaign, Illinois. He was on the Attending Staffs of the Burnham City Hospital and the Mercy Hospital, and served as Civilian Consultant in Internal Medicine at the Chanute Air Base in Rantoul, Illinois.

Dr. Westra was an Associate of the American College of Physicians (1945), a Diplomate of the American Board of Internal Medicine, and a member of Sigma Xi and Alpha Omega Alpha. In 1948 and 1949, he was Secretary of the Champaign County Medical Society, and during this time he was very active before the public of his community as an opponent of the proposed compulsory national health insurance legislation. His loss to the community is greatly felt. He was a respected clinician, teacher and leader.

CHARLES H. DRENCKHAHN, M.D., F.A.C.P.,  
Governor for Southern Illinois

# ANNALS OF INTERNAL MEDICINE

VOLUME 31

DECEMBER, 1949

NUMBER 6

## THE ETIOLOGY AND MANAGEMENT OF THE HEMORRHAGIC DIATHESSES \*

By CHARLES A. DOAN, M.D., F.A.C.P., *Columbus, Ohio*

HEMORRHAGE uncontrollable except by expert medical management, may present in the practice of any physician at any time. Under normal conditions, the integrity of the vascular system and the circulating fluidity of the blood reflect a nice physiologic balance in an exceedingly sensitive and complicated coagulation mechanism. The physical-chemical intricacies of normal blood coagulation continue to challenge the best thought of many investigators and to stimulate ever more detailed experimentation in many laboratories, in the attempt to better understand and to more effectively solve the clinical problems centering about abnormal hemorrhage. The concepts and terminology arising from parallel efforts in different laboratories have resulted in much confusion among clinical diagnosticians regarding the interrelationships of the basic coagulation phenomena themselves. The first prerequisite, therefore, in approaching this field is a definition of terms, currently presumed to be interchangeable, as they have been coined to describe the observed sequence of events in normal blood coagulation (Graph A, page 981—modified after Quick) the exact chemical factors concerned having not yet been isolated.

It is now agreed that both platelets and plasma factors are essential for completely physiologic blood coagulation, Brinkhous and Conley each having demonstrated the lack of spontaneous coagulation of blood plasma for long periods when blood is carefully collected in silicone (methylchlorosilane) coated tubes, the blood platelets being promptly separated and the plasma stored at low temperatures ( $4^{\circ}\text{C}$ ). Quick has hypothesized the liberation of an enzyme, thromboplastinogenase, from disintegrated platelets, which is essential for the conversion of plasma thromboplastinogen to thromboplastin (thrombokinase). Injured tissue may also be the source of thrombo-

\* Presented as a Morning Lecture at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 21, 1948. Received for publication September 8, 1949.

plastin. It is believed that the platelets release a second enzyme which promotes vasoconstriction of the local capillary bed as an aid in prompt coagulation. The plasma thromboplastinogen of Quick is identical with the anti-hemophilic globulin of Fraction I of Cohn, as extensively studied by Taylor and associates.

Prothrombin (a large molecular glycoprotein) is thought to be present in plasma in both a free and combined form (prothrombinogen) and it is suggested in the chart by the broken line that plasmin may be one of the accelerators of the production of free prothrombin from prothrombinogen. The reaction between thromboplastin and prothrombin has been shown to be stoichiometric, therefore the consumption of prothrombin may be measured in any given coagulation reaction and is directly proportional to the amount of thromboplastin available, which in turn is a function of the available platelets. Dicumarol's anticoagulant effect is mediated through a lowering of the plasma prothrombin level. Ionized calcium is a catalytic essential in this second phase of blood coagulation and it is by the inactivation of these ions that sodium citrate or calcium oxalate prolong the fluidity of shed blood.

Seegers and associates have noted that mixtures of purified prothrombin, thromboplastin and calcium ion produce only 30 to 40 per cent yield of thrombin in one to one and one-half hours, whereas, when plasma previously activated with thrombin is added, the period of slow thrombin production is reduced to about two minutes and the yield is 100 per cent. They attribute this to the presence of an accelerator globulin, Ac-globulin, inert in plasma but promptly converted to active catalytic serum Ac-globulin in the presence of thrombin. It now seems probable that Seegers' Ac-globulin is identical with Quick's prothrombin A (the latter's prothrombin B being true prothrombin). Owren's factors V and VI are closely identified with, if not actually, Seegers' Ac-globulin and Quick's prothrombin A, in accomplishing the second phase of coagulation.

The third phase in blood coagulation remains unchanged from earlier concepts in that thrombin interacts with the plasma fibrinogen to form the fibrin clot. It is at this point that heparin inhibits prothrombin conversion and the thrombin-fibrinogen reaction and thereby prolongs blood coagulation. Retraction of the clot in time and degree is directly proportional to the excess of platelets which may be present; as the number of platelets is diminished the speed of prothrombin consumption is decreased, and below a critical level, which varies in different patients, a serious defect in coagulation is present, though masked by a normal coagulation time (Quick). Thrombin, itself, has a "labilizing influence" on the blood platelets, so that with the first thrombin formed in a given coagulation system, there is an acceleration in the speed of release of thromboplastinogenase with more rapid clot formation in the presence of an adequate supply of platelets.

Fibrinolysis, the dissolution of blood clots, is exceedingly important from a clinical standpoint. It is now established that there is present in normal plasma an inactive precursor of plasmin termed plasminogen. Plasmin is

a synonym for the proteolytic enzyme activity which has been known variously as serum trypsin, serum tryptase, serum protease, fibrinolysin and thrombolysin. The streptococcic filtrate factor comparable in action on plasminogen or plasmogen has been called streptokinase, and the antibody-like resistance which may be demonstrated in certain patients recovered from streptococcic infections has been designated antistreptokinase. In the albumin fraction of plasma has been found an inhibiting enzyme, antiplasmin (Macfarlane).

Obviously a clinical bleeding tendency may occur under a wide variety of pathologic circumstances, and be influenced by one or more of many potential factors acting at any one of the many points in the complex mechanism of blood coagulation. The first clinical sign may appear and re-appear as an asymptomatic transitory purpuric manifestation, apparently limited to skin or mucous membranes, or the syndrome may present as one of the most acute, fulminant and critical emergencies with which the physician is ever called upon to deal. The specificity, and therefore the success of the therapeutic regimen advised, is directly dependent upon the preciseness and exactitude, and, in the acute purpuras, the promptness of the differential etiologic diagnosis in any given patient.

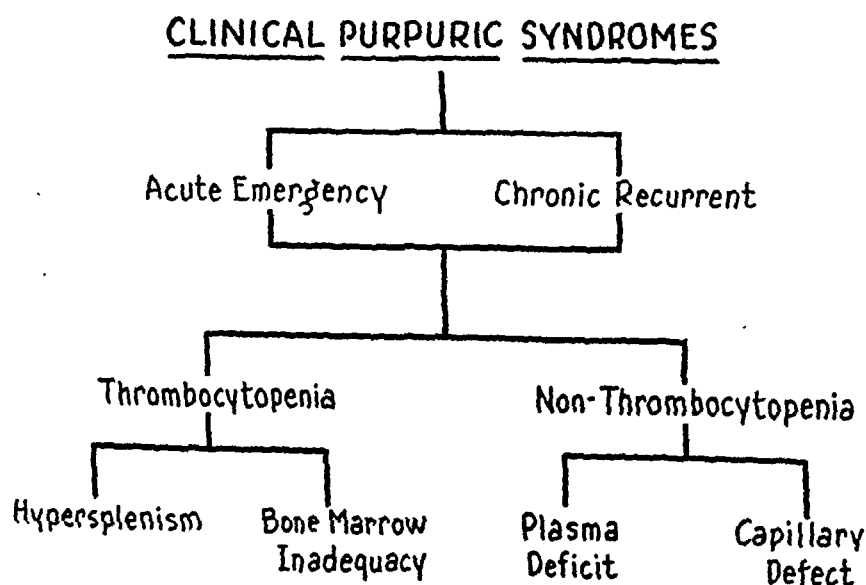


FIG. 1.

The approach to an understanding of the particular mechanism involved can best be made systematically, keeping in mind certain rather broad principles which underlie the hemorrhagic diatheses (figure 1). When a true purpuric extravasation of blood has been identified by its color, character and permanence, or if persistent bleeding occurs other than in the skin, it at once becomes essential to know whether the thrombocytes are normal or are decreased in the peripheral circulation.

## THROMBOCYTOPENIC PURPURA

If and when few or no blood platelets are to be found in the circulating blood of any patient with clinical purpura, a study of the bone marrow is essential to determine whether this deficit is secondary to (1) a relative or absolute central (bone marrow) megakaryocytic inadequacy, or, (2) an excessive peripheral (splenic) demand (figure 2).

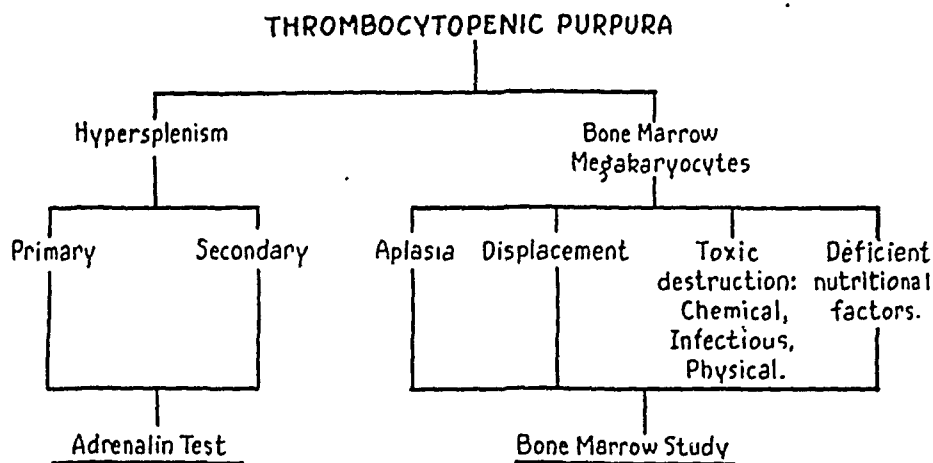


FIG. 2.

*Thrombocytopenic purpura due to defective bone marrow.*

*Primary Marrow Aplasia.* Generalized purpura is frequently the first sign of progressive marrow hypoplasia. When, upon repeated bone marrow studies, obtained from the manubrium and the body of the sternum, from selected spinous processes and from the crest of the ileum, no megakaryocytes are found, plus definite evidence of a beginning marrow pancytopenia,—and when neither past personal history nor direct investigation reveals toxic environmental, medicinal or bacterial factors, primary hypoplasia with or without an osteofibrosis or osteopetrosis mechanism may be established. In a certain proportion of such patients extra-medullary hematopoiesis in spleen and liver may partially compensate for the marrow hypoplasia. Do not misinterpret the significance of splenomegaly in these cases, even when evidence of periodic hypersplenism is obtained. In the early stages, with only moderate marrow hypoplasia and in the proved absence of ectopic splenic hematopoiesis, splenectomy, in carefully selected patients, may be followed by a remission of months or years.

Supportive replacement of fresh citrated blood transfusions (not "bank blood" more than 24 hours old), selected, typed and carefully matched, is the treatment of choice. Polycythemic donors, in our experience, have made particularly effective blood contributions to such patients, inducing in some instances more prolonged remissions than have normal donors (figure 3). Though such has never happened to our knowledge, if the transmission of a

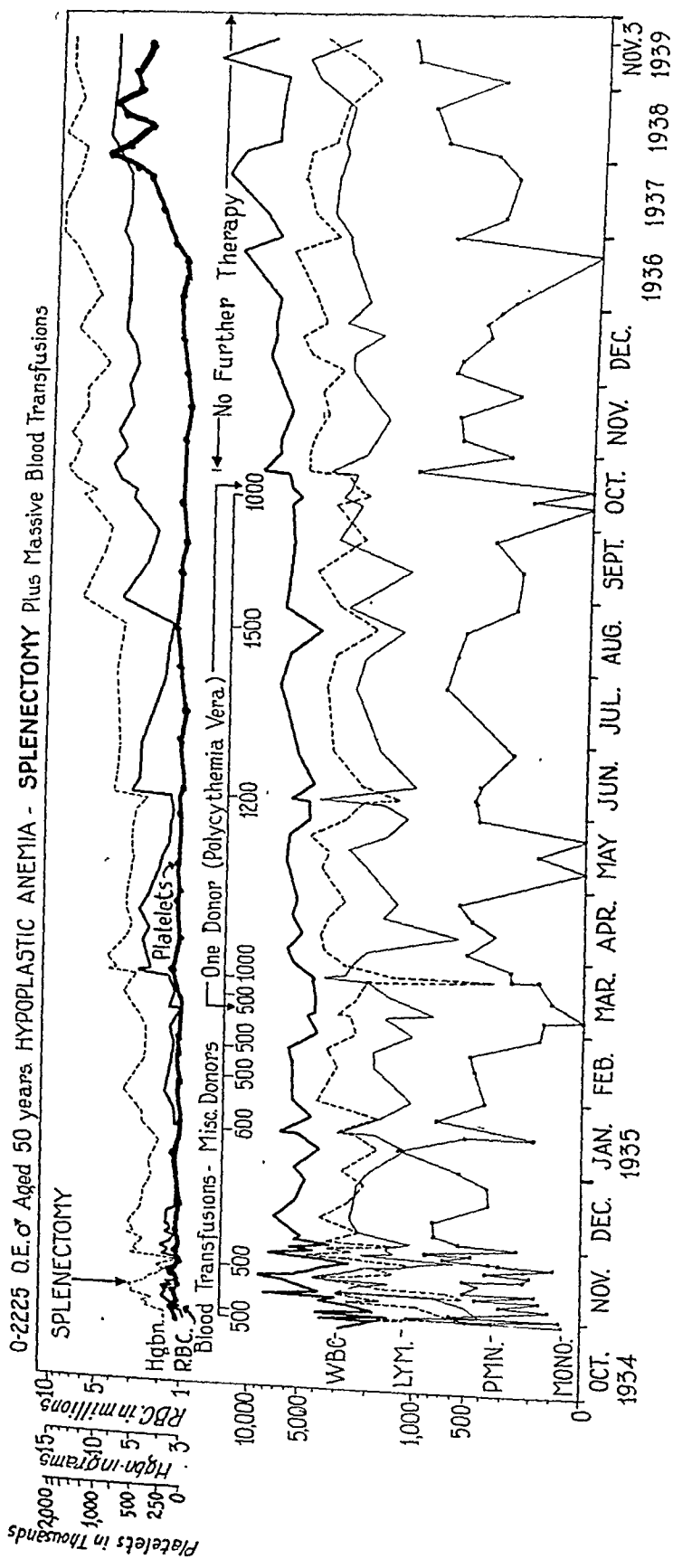


FIG. 3.



pan-marrow hyperplasia to patients with a primary marrow aplasia could be accomplished, it should lead to a longer and more readily controlled life than now is possible in progressive aplastic anemia.

The generous use of any or all of the presently known stimulatory and maturing factors for blood cells—liver, folic acid, vitamin B<sup>12</sup> et al.,—have, thus far, failed to affect marrow regeneration in this type of patient, though theoretically and experimentally nutritional deficiency does at times result in progressive marrow hypoplasia.

*Nutritional Deficiency Marrow Hypoplasia.* In addition to the now well-known vitamin components from the B and C complexes, the E.M.F. from liver extract, and the trace mineral catalysts, copper and cobalt, it is recognized that certain amino acids are also essential to optimum hematopoiesis. Under certain naturally occurring circumstances, in individuals with food idiosyncrasies, or gastrointestinal abnormalities concerned with disturbed digestion and absorption, thrombocytopenic purpura on a deficiency basis secondary to general marrow hypoplasia, may occur. The correction of any specific deficiency will be followed by the regeneration of megakaryocytes and the disappearance of all purpuric manifestations.

*Toxic marrow destruction or inhibition* may result from industrial chemicals (see benzol, figure 4), therapeutic drugs (see Sedormid, figure 5), physical agents, roentgen-ray and radioactivity, virus and bacterial infections. Careful supravital study of the fresh living marrow in thrombocytopenic purpura will at once reveal clearly and unequivocally any specific damage to the megakaryocytes which may be responsible for the circulating platelet deficit. Vacuolated nuclei and cytoplasm with chromatin karyorrhexis and increased phagocytosis of specific cellular debris are unmistakable evidences of such toxic damage. The case history and other pertinent data will establish the specific antigenic or direct toxic agent in each instance. Immediate removal or discontinuance and elimination of the offending agent, accompanied by supportive fresh blood transfusions containing viable platelets, will permit the regeneration of megakaryocytes and thrombocytopoiesis in a time relationship proportional to the severity and duration of the toxic influence. If complete recovery does not result, splenectomy in selected instances is followed by marrow recompensation (figure 4).

In infections, clinical purpura may be due to central marrow toxemia as just described, or to bacterial emboli, or to capillary endothelial damage. Intensive specific chemo- or antibiotic therapy, 200 to 500 mg. vitamin C daily, frequent (q. 8 hrs.) small (200 c.c.) fresh blood transfusions, with 24 hour supportive nursing care, will usually result in recovery.

*Myelophthisic (Displacement) Thrombocytopenia.* The bone marrow study in some patients with thrombocytopenic purpura will reveal the first evidence of foreign cell invasion at the expense of megakaryocytes and eventually of the other normal marrow elements. Therapy is dependent upon the type and character of the cellular hyperplasia. The various leukemic states, more particularly acute monocytic leukemia and leuko-lympho-

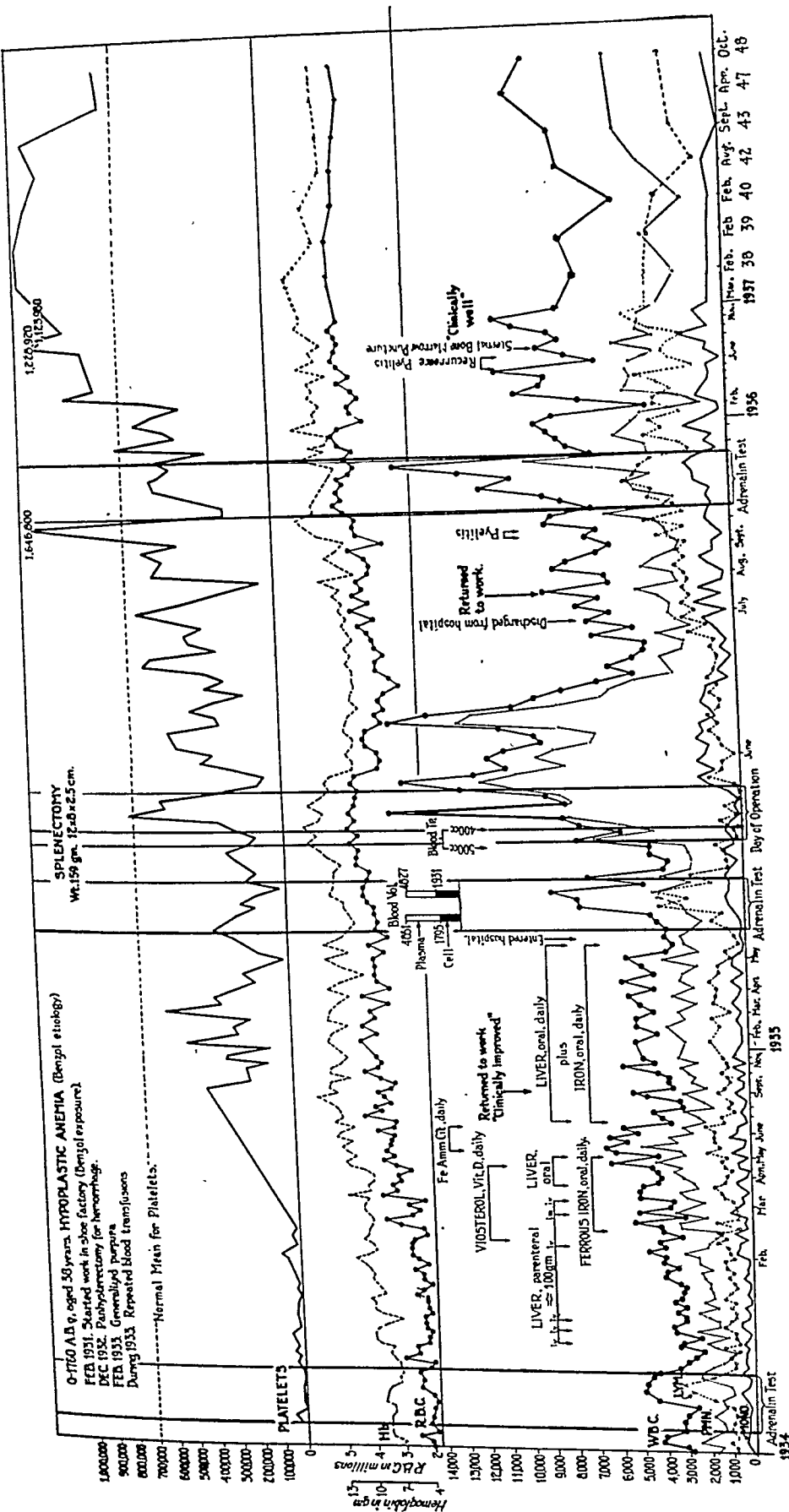


FIG. 4.

sarcoma (acute lymphatic leukemia) may be ushered in with a clinical purpuric syndrome. Fresh blood transfusions and antibiotic chemotherapy are indicated initially, until the more or less specific anti-leukemic agents (the nitrogen mustards, folic acid antagonists, urethane) now available have had the time interval required to inhibit and destroy the displacing cellular units and permit normal hematopoietic regeneration. Multiple myeloma, osteo-Hodgkin's and metastatic carcinoma may be clinically initiated by thrombocytopenic purpura. The specific treatment of such purpuras, *due to marrow involvement* is the fundamental treatment of the principal disease.

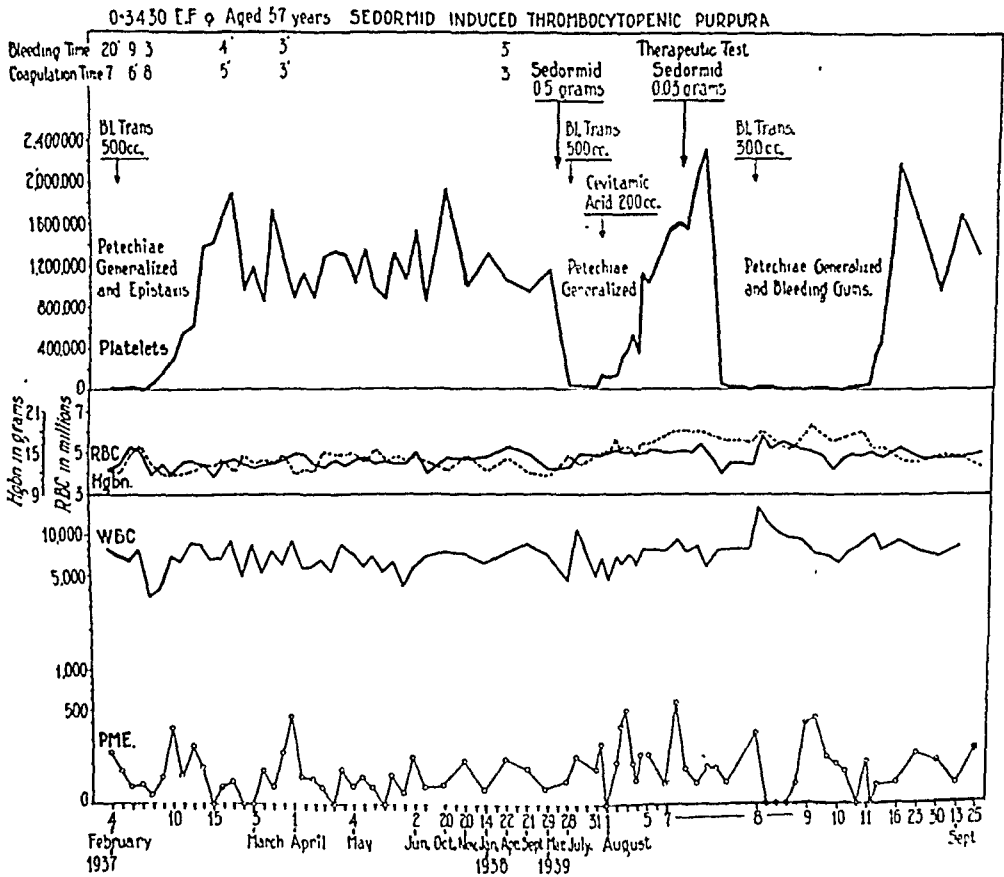


FIG. 5.

*Thrombocytopenic Purpura Hemorrhagica—Hypersplenism.* When peripheral thrombocytopenia has been found associated with clinical purpura and the bone marrow studies not only have failed to reveal any evidence of cellular aplasia, displacement, damage, or toxicity, but actually reflect an excessive multiplication of megakaryocytes in all stages of immaturity,—the more mature units showing active cytoplasmic platelet fragmentation in the living supravital preparations,—the conclusion is justified that despite the apparently uninhibited compensatory megakaryocytic hyperplasia, the peripheral platelet demand is in excess of the available supply. When the spleen

is *not* demonstrably enlarged, *primary splenic thrombocytopenic purpura* is the most likely diagnosis.

*Primary Hypersplenic Thrombocytopenic Purpura (Werlhof's Disease).* In the absence of any other demonstrable pathologic mechanism, specifically bone marrow damage or inadequacy, the adrenalin test may reveal an hypersequestration of platelets by a normal sized spleen indicative of a primary specific withdrawal or inhibition of circulating platelets (figure 6). Note that the postsplenectomy adrenalin test failed to reveal the hypersequestration

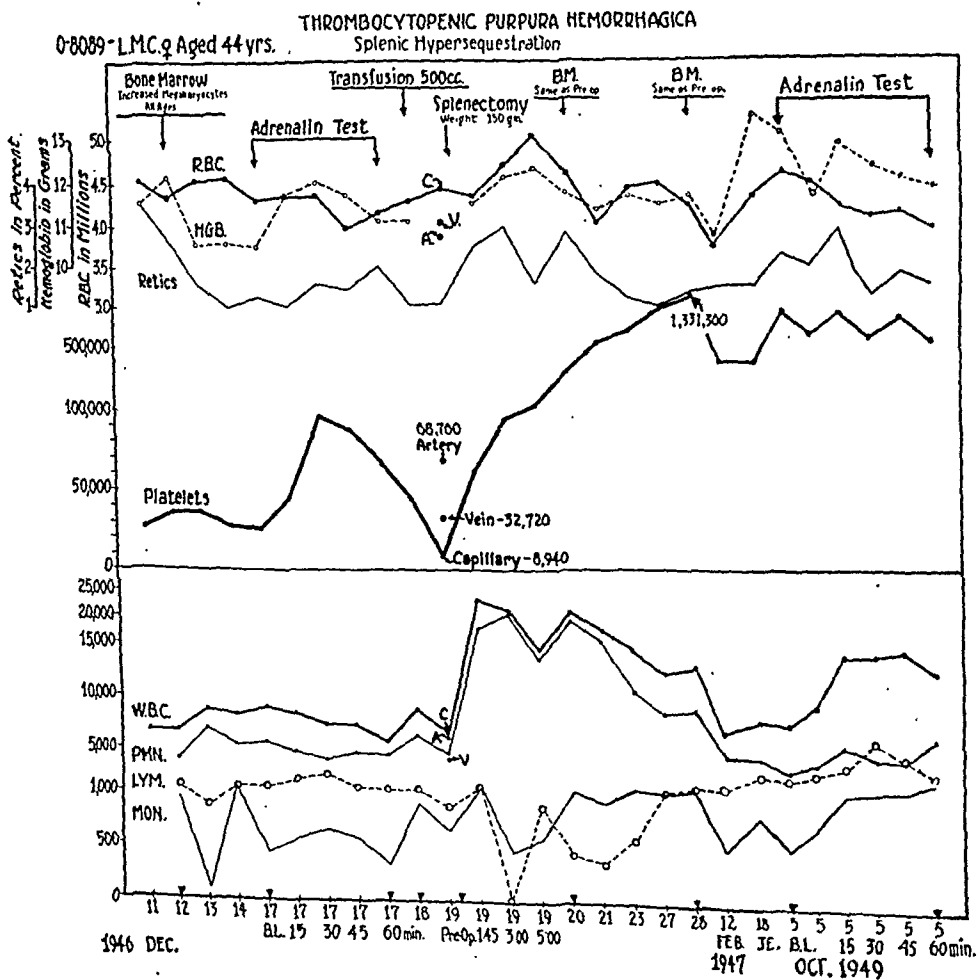


FIG. 6.

of thrombocytes, so well demonstrated during the purpuric episode. The clinical manifestations may be relatively benign, chronically recurring, chiefly cosmetic in the showering of skin petechiae, or they may develop suddenly and involve multiple critical hemorrhages involving mucous membranes of nose and mouth, gastrointestinal tract, genito-urinary system, uterus, and central nervous system. In the acute episode there may be time only for peripheral blood and bone marrow diagnostic studies. When there is severe headache, stupor, or other signs of increased pressure due to intracranial

hemorrhage, careful decompression via spinal puncture should be promptly accomplished. Multiple emergency *fresh* blood transfusions may be necessary to replace acute blood loss and prevent imminent shock, as well as to supply platelets in the attempt to control further blood loss.

Whether the syndrome is chronic *or* acute, splenectomy is the only effective therapeutic procedure for this mechanism. A particularly careful search for accessory splenic tissue should be made at the first surgical exploration—including a liver biopsy and a mesenteric lymph node specimen for immediate histologic study and future reference. An hypersplenic relapse may be precipitated by as little as 5 grams of splenic tissue in patients having this trait (figure 7). When faced with such a clinical and hematologic recurrence, it is entirely justifiable to attempt to locate aberrant splenic tissue by thorotrast visualization. Once again surgical removal is the only known effective therapy. When a generalized hyperplasia of hyperfunctioning reticulo-endothelial cell phagocytes occurs in the liver and lymph nodes, complete surgical excision is obviously impossible and conservative measures, chiefly serial blood transfusions are at the present time the only treatment. Irradiation, vitamins, snake venom, parathormone, calcium, rutin, have all proved ineffective in this clinic, in this type of case.

*Secondary Hypersplenic Thrombocytopenic Purpura.* When there is an obvious enlargement of the spleen with adrenalin test evidence of specific platelet hypersequestration, and the bone marrow shows only compensatory megakaryocytosis without myelophthistic or toxic marrow damage, a hypersplenic syndrome secondary to some other disseminated constitutional disease must be considered. Primary splenic Hodgkin's granuloma, splenic Gaucher's disease, chronic leukemic involvement of the splenic parenchyma by any cell type, tuberculosis or tertiary lues of the spleen, congestive splenomegaly secondary to myocardial decompensation, acute splenic tumor of infectious etiology,—all have been observed to be associated on occasion with a more or less acute hypersplenic thrombocytopenic purpura in which the bone marrow may be excluded as a contributing factor. Under such circumstances emergency splenectomy should be performed on exactly the same reasoning as for primary hypersplenism, irrespective of the known presence elsewhere in the body of a serious disease process. The immediate danger without surgery is fatal hemorrhage; the more remote danger of progressive constitutional disease may better be met by whatever specific therapy is available after the hypersplenic complication has been permanently eliminated. With modern anesthesia and expert surgical technic, the risk of surgery in these patients is far less than the dangers of spontaneous fatal hemorrhage or of a surgically induced exacerbation of the basic disease process. One successful facing of such a crisis will convince the doubtful of the rationale here advocated.

An obese white male patient presented with an acute purpuric syndrome. Initial studies showed an absolute peripheral thrombocytopenia and a typical bone marrow with compensatory megakaryocytic hyperplasia as the only cellular abnormality

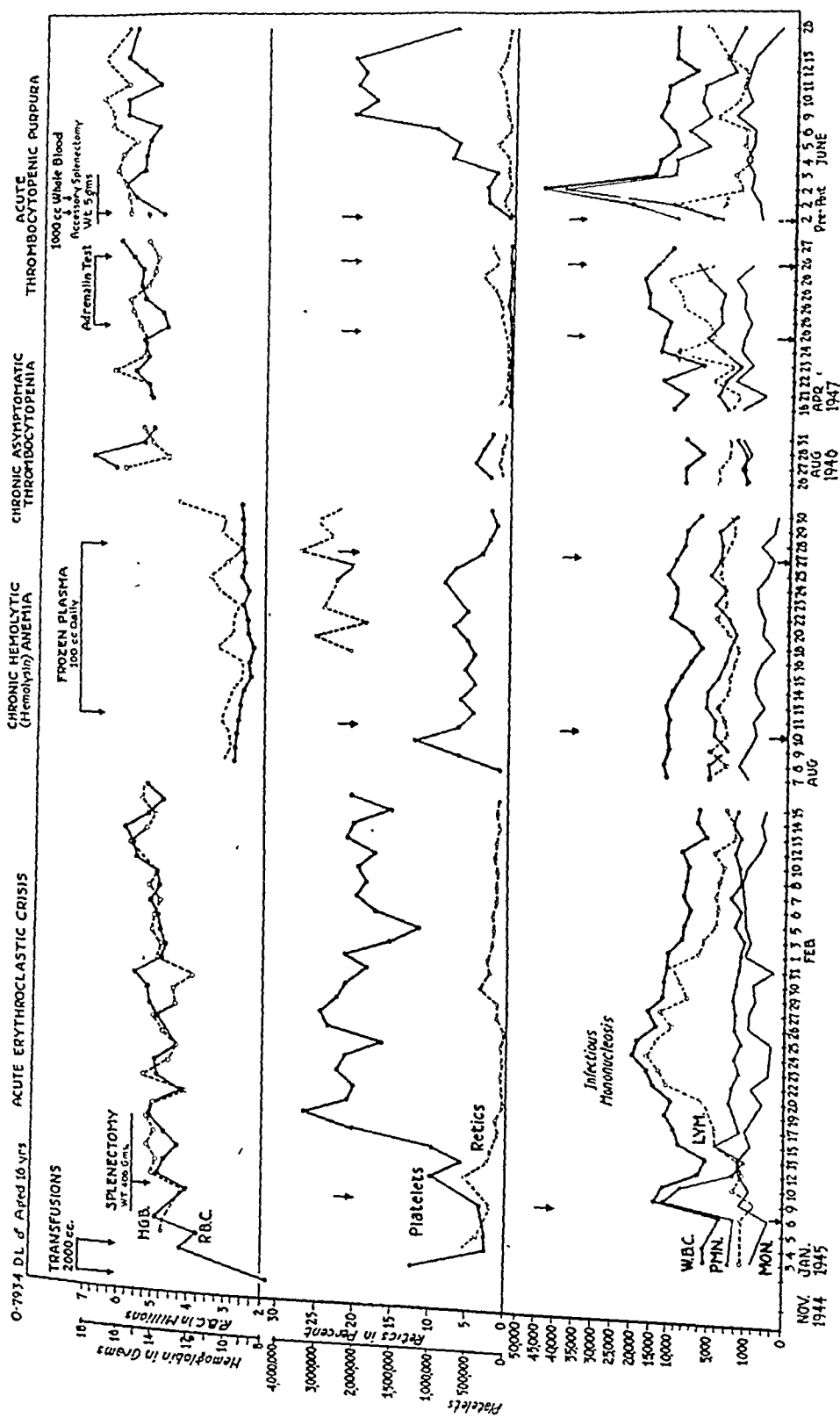


FIG. 7.

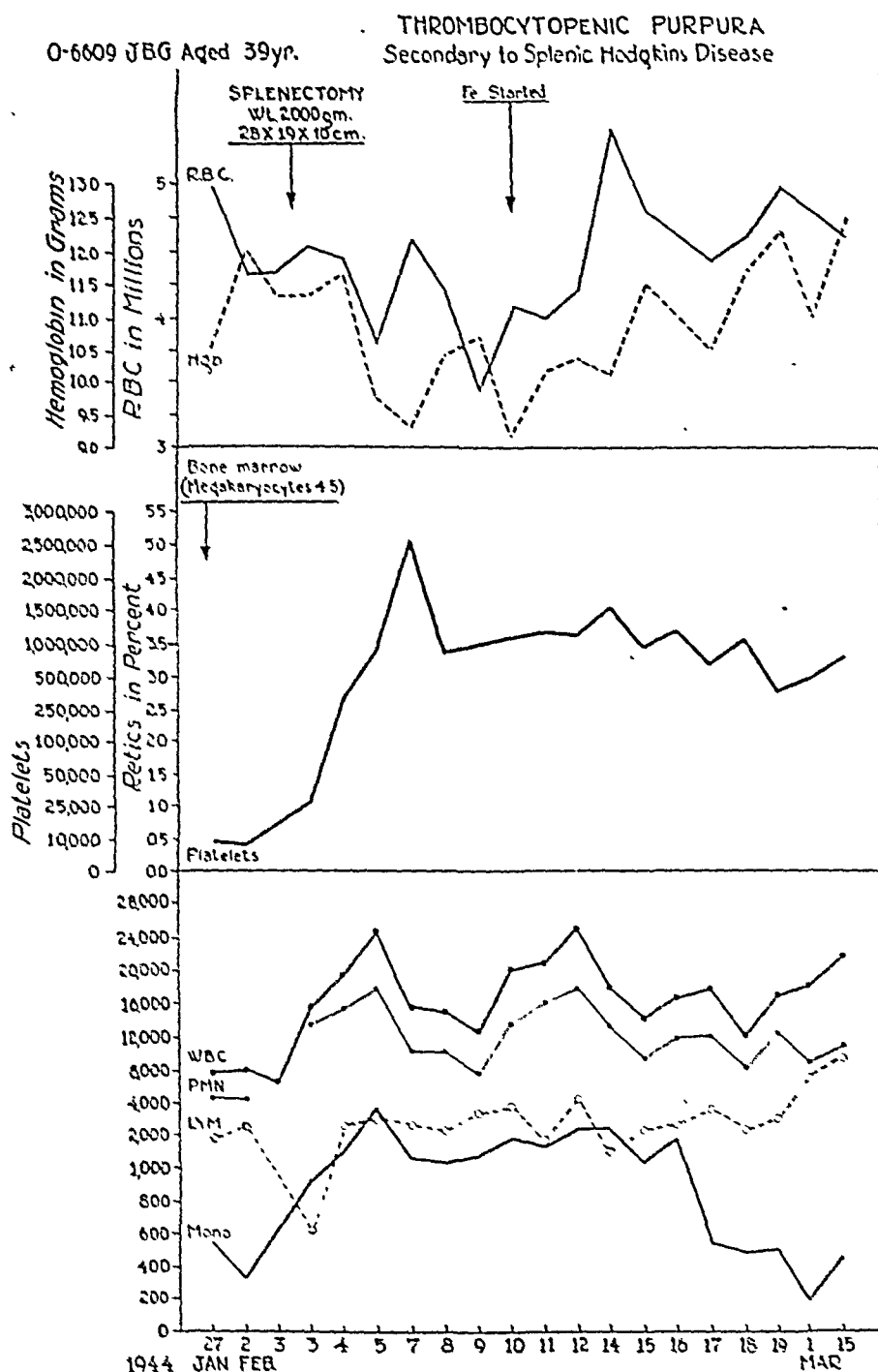


FIG. 8.

(figure 8). Neither spleen nor liver could be palpated and all plasma coagulation factors and routine blood chemistry studies were found to be within physiologic limits. A diagnosis of primary splenic thrombocytopenic purpura was made and immediate surgery advised. Supported by fresh whole blood transfusions, an emergency surgical exploration was accomplished. An enlarged spleen was found and removed.

without evidence of liver or lymph node involvement. On supravital and fixed section study the pathology of Hodgkin's granuloma was revealed, apparently primary in the spleen. The specificity of the hypersequestration of platelets by this Hodgkin's involved spleen was proved by the dramatic and immediate rise in circulating platelets with improved blood coagulation, which was evident during the completion of the operation. Though unsuccessful in removing the sole focus of Hodgkin's, as we had hoped, other manifestations of the disease developing during the ensuing 18 months—there was never any recurrence of the thrombocytopenia or purpuric complications.

O-8887 55 ♀ AGED 12 YRS. THROMBOCYTOPENIC PURPURA  
 1 Acute Rheumatic Fever with Cardiac Damage.  
 2 Bronchopneumonia → Acute Cardiac Failure.  
 3 Congestive Splenomegaly → Acute Hypersplenism.  
 4 Thrombocytopenic Crisis → Generalized Purpura  
 5 Bone Marrow Hyperplasia sans Toxic Damage

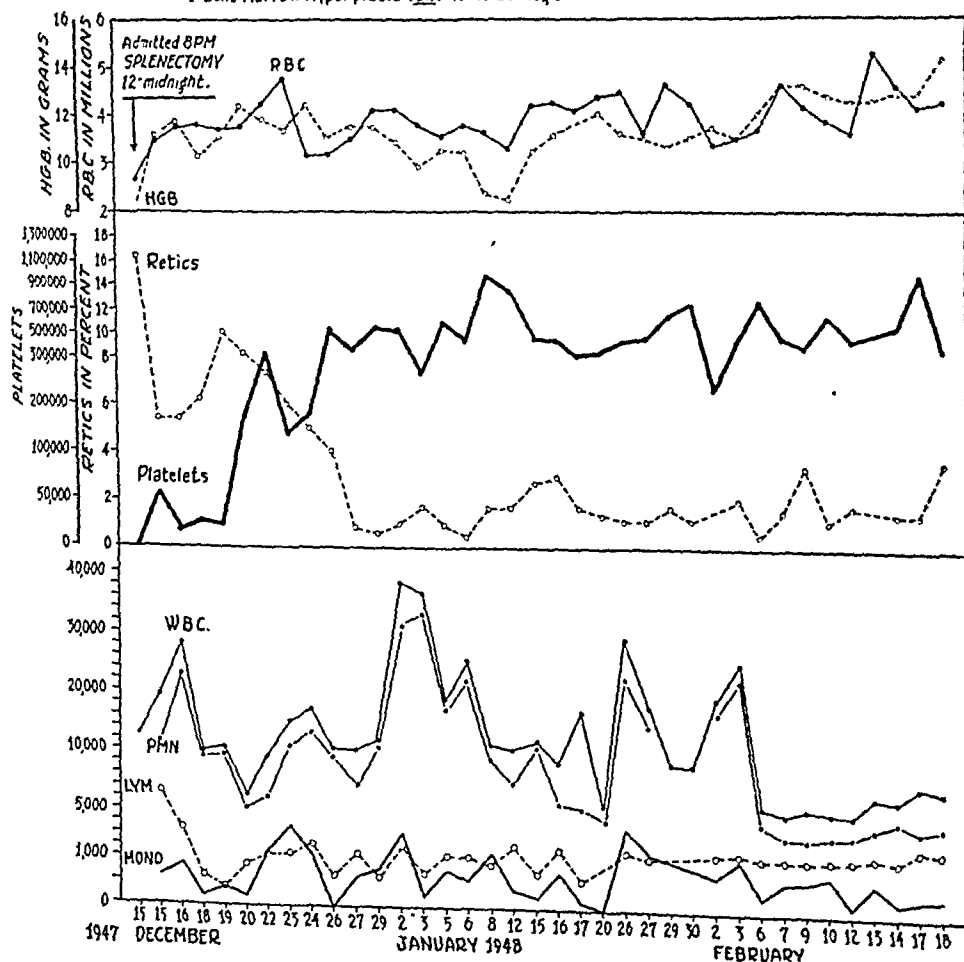


FIG. 9.

A young girl, aged 12 years, was admitted to the University Hospital as an acute emergency with generalized purpura, persistent epistaxis and gastrointestinal and genito-urinary hemorrhages of three days' duration (figure 9). Repeated fresh whole blood transfusions, prior to admission, had failed to control the hemorrhagic diathesis even temporarily. An acute upper respiratory infection with bilateral pneumonitis had preceded the bleeding manifestations and a toxic etiology, bacterial or chemotherapeutic in origin was suspected. Peripheral blood studies confirmed the complete absence of circulating platelets, and a coincidental supravital survey of the bone-



marrow showed a pan-marrow hyperplasia, without any evidence of toxic cellular destruction or inhibition. The megakaryocytes were particularly observed to be multiplying and maturing and fragmenting their cytoplasm into platelets at a greatly accelerated tempo. Examination of the chest confirmed the existence of pneumonic involvement; the heart was greatly enlarged with systolic and diastolic mitral murmurs; both spleen and liver were enlarged and tender to palpation; and there was pedal, facial and sacral edema.

A history of acute rheumatic fever explained the mitral lesion and provided a plausible explanation for the evidence of cardiac decompensation. There was no family history of any hematologic dyscrasia. A tentative diagnosis of acute splenic thrombocytopenic purpura was made, the sequence of events probably being acute rheumatic fever with residual cardiac damage, plus superimposed bilateral pulmonary infection with acute congestion and hemostasis in an unstable spleen as the heart began to fail. The patient was in extremis. Fresh whole blood transfusions were started simultaneously in two extremities and within four hours of her hospital admission, the spleen had been removed and normal coagulation reestablished with plenty of platelets demonstrable in the circulation. The clinical improvement was equally dramatic even before chemo- and antibiotic therapy had had the opportunity to control fully the pulmonary and renal infections and digitalization the cardiac edema. Recovery was uneventful and has continued to the present time.

*Prophylactic splenectomy* should be advised and undertaken whenever a hypersplenic syndrome has been observed, either as a chronic or as an acute episode, even though one or more spontaneous remissions have intervened. The spleen is, at best, an unstable reservoir for platelets and for all of the other normal circulating blood cell elements and once it has been caught in any pathological hyperactivity, it is never again to be fully trusted. Sudden acute hemoclastic crises will usually recur, sooner or later, either spontaneously or precipitated by minor illnesses or accidents. Since the spleen is not essential to either normal human health or longevity, there are no known contraindications to its removal at any age. Chronic invalidism and acute fatalities are, on the other hand, more frequently the result of a pathologic spleen than has heretofore been generally realized.

#### NON-THROMBOCYTOPENIC PURPURA

If and when normal or excessive numbers of qualitatively normal platelets are to be found in the circulating blood of any patient with clinical purpura immediate studies are indicated to differentiate between (1) specific plasma and/or (2) specific capillary defects (figure 10).

*Plasma Coagulation Defects.* The humoral or chemical factors initiating and inhibiting blood coagulation continue to present a most complex problem even to the expert investigators in this field. While tremendous progress has been made in the understanding and control of this vital series of coagulation phenomena the final chapter has not yet been written and, therefore, the complete control of all purpuric syndromes has not been attained (Graph A).

*Hypoprothrombinemia.* It is now routine to determine the prothrombin plasma level in every patient showing any hemorrhagic tendency and to maintain it at high normal levels, if possible, irrespective of the rôle which may be

played by other mechanisms. Low prothrombin levels have been shown to be responsible for purpura in "melena neonatorum" or "hemorrhagic disease of the newborn" (as low as 5 per cent of normal adult level); in obstructive jaundice, the absence of bile from the intestinal tract interfering with optimum absorption of the fat-soluble vitamin K; in liver disease sufficiently severe to interfere with its important function of prothrombinogenesis from vitamin K; in individuals on a low vitamin K diet; and in patients with hyperperistalsis or other intestinal pathology preventing proper vitamin K absorption.

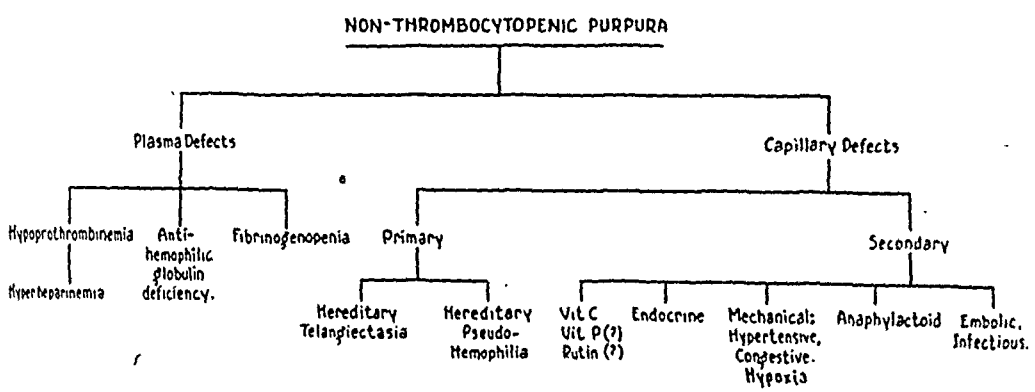
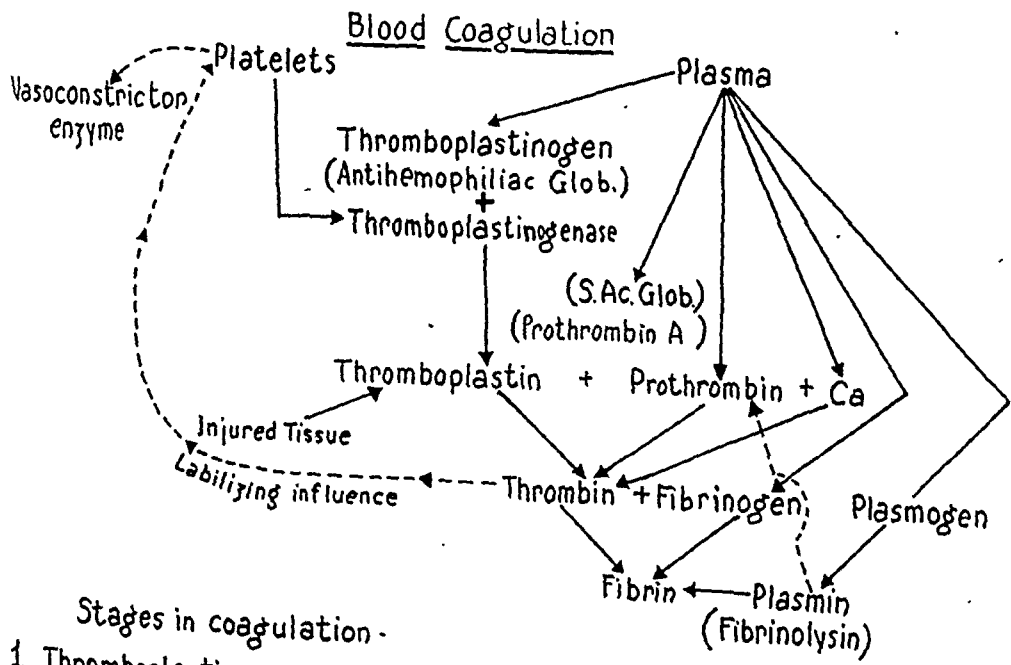


FIG. 10.



- Stages in coagulation -
1. Thromboplastinogen + platelet enzyme → thromboplastin
  2. Prothrombin + thromboplastin + Ca = thrombin
  3. Fibrinogen + thrombin → fibrin

Modified after Quick

GRAPH A.

Synthetic derivatives of quinone have largely replaced the earlier concentrates of alfalfa extract and may be administered by any route, the dosage and strength of the various preparations being easily adjusted to the age of the patient and the severity of the hypoprothrombinemia. The water-soluble compound 4-amino-2-methyl-1-naphthol may be given to newborn infants in 1 mg. doses either intramuscularly or intravenously and repeated at six hour intervals until the symptoms are controlled. The water-insoluble 2-methyl-1,4 naphthoquinone is the most active preparation and may be given by mouth 2 to 5 mg. daily with bile salts or intramuscularly 2-4 mg. daily. Menadione, U.S.P., 2-methyl-naphthoquinone, has a daily oral dose of 1 mg. Only in the presence of extensive liver damage will this medication fail to restore the prothrombin promptly to normal levels and thus control the hemorrhagic diathesis due to this deficiency.

Small repeated fresh blood transfusions may be used to supply prothrombin directly in the newborn, and somewhat less effectively in adults. The prothrombin supplementing capacity of human blood decreases rapidly during blood bank storage.

*Hyperheparinemia.* Spontaneous coagulation of the blood within the circulation is prevented by the presence of heparin in physiologic concentration, acting through an inhibition of prothrombin conversion and the thrombin-fibrinogen reaction. Allen and associates have recently attributed prolonged bleeding following extensive irradiation and following the administration of cytotoxic drugs, such as the nitrogen mustards, to the presence of an excess of heparin or heparin-like substances, in addition to the thrombocytopenia which develops. Appropriate tests must be made whenever this mechanism is suspected. Protamine and toluidine blue dye have been more or less effective in controlling the hemorrhagic phenomena due to the hyperheparinemia. The recommended dosage of protamine is 0.5 to 2.0 mg. per kg. body weight, in 50 to 75 c.c. NaCl intravenously, each 24 hours, though toxic reactions may follow its administration in some patients. The toluidine blue dye is prepared and administered similarly, 1 to 4 mg. per kg. body weight. It may be repeated for several days and is usually well tolerated.

The thrombocytopenic components in this radiation-induced hemorrhagic diathesis must be supplied by repeated *fresh* whole blood transfusions until the marrow has recovered.

*Anti-Hemophilic Globulin Deficiency.* Ordinarily it is not difficult to recognize the male victim of a hemophilic heritage but frequently the differential diagnosis between a chronically recurring thrombocytopenic purpura and a mild, but true, hemophiliac requires considerable investigation, thought and observation. The wide difference in rationale of treatment in these two hemorrhagic diseases obviously demands precise diagnosis.

When the objective establishment of a recurring, if not constantly demonstrable, abnormally prolonged coagulation time, without thrombocytopenia has given circumstantial evidence of a "globulin defect" prophylactic therapy

may be necessary for the prevention of spontaneous hemorrhages in the normal course of living, and preceding elective surgery; or in the presence of trauma or emergency surgery rigid temporary control of the coagulation time may be mandatory, even life-saving.

Fresh whole blood, fresh plasma, or freshly frozen or lyophilized plasma obtained from "normal" donors, contains antihemophilic globulin, which will reduce the prolonged in vitro coagulation time of the blood from a hemophilic patient more or less to normal at once and for a variable period of time. The amount required and the frequency of readministration depend upon so many uncontrollable variables that only regularly repeated coagulation tests on carefully obtained samples of venous blood may determine these data for each individual patient, especially in times of critical need.

Plasma Fraction I of Cohn contains the largest increment of anti-hemophilic globulin, and may be used entirely effectively. It is available through the National American Red Cross. Again, however, no standard dosage can be recommended, (1) because of the variability of the potency of each lot prepared; (2) because of the variability in the hemophilic patient's own need from time to time; and (3) because of the greater antigenicity of Fraction I than whole blood.

Unless the very occasional patient should develop a specific "antibody-like" resistance to transfused normal human globulin, the sources of anti-hemophilic globulin, including fresh normal whole blood or human plasma are now such as to make possible the approach to this problem today with some equanimity and a greater assurance of success. In the more acutely susceptible individuals a regimen of regular prophylactic supplements of antihemophilic globulin-containing plasma may be established on a one to three day basis with some promise of success.

*Fibrinogenopenia.* The normal human plasma fibrinogen level ranges from 0.2 to 0.4 gm. per cent. Afibrinogenemia occurs rarely as a congenital and usually as a familial disease with the hemorrhagic tendency becoming apparent, and therefore, dangerous, only secondary to trauma. Fresh blood or plasma transfusions may be effectively used to supply the fibrinogen deficit.

Fraction I of Cohn contains the fibrinogen portion of the plasma and Diamond has reported its successful use as a prophylactic in the satisfactory control of patients with this defect when given regularly, for example in one of his patients, every three days. Each patient must, of course, be studied individually for dosage and frequency.

#### *Capillary Defects Resulting in Clinical Purpura.*

*Primary Hemorrhagic Telangiectasia.* Hereditary telangiectasis is a rather common, usually benign, hereditary abnormality, its pin-head sized or larger nodular vascular tumors and spider angiomas being more frequently of cosmetic than hemorrhagic concern. The bright red compressible capillary tufts in skin and mucous membranes have often been mistaken for the petechiae of true purpura on superficial examination. There is, however, no

thrombocytopenia and no demonstrable plasma coagulation defect, but only dilated capillary and venous sinusoidal fragility, responsible for the spontaneous hemorrhages which occur with increasing frequency with age, and which may cause chronic invalidism or even threaten life, itself, at times.

Obliterative cauterization of particularly susceptible localized tufts in the mucous membranes of nose and throat is the treatment of choice. High vitamin C and adequate vitamin K are essential prophylactic supplements. Blood transfusion is an emergency supportive measure, as in all hemorrhage.

*Hereditary Pseudohemophilia.* We place this bisexually-occurring, hereditary, hemorrhagic dyscrasia under the category of "primary capillary defect" since no qualitative or quantitative thrombocyte and no plasma coagulation defects have been discovered to account for the severe and sometimes fatal hemorrhages. No obvious hemangiomas occur, but Macfarlane of Oxford, England, has demonstrated the apparently inherent inability of the capillary wall in these patients to contract following injury. This mechanism leads to that very rare phenomenon of a *prolonged bleeding time* in a patient with non-thrombocytopenic purpura. Fresh whole blood transfusions give the best results and usually suffice though they do not alter either the normal coagulation or the prolonged bleeding times in these recipients. High vitamins C and K, avoidance of all unusual and unnecessary trauma, and maximum transfusion support and meticulous hemostasis by multiple ligation during emergency surgery are axiomatic.

*Secondary Capillary Defects.* Scurvy has long been known for its hemorrhagic manifestations, and there is no good reason for avitaminosis C to exist in modern society. Nevertheless, it occurs just often enough in the least expected places, in patients with food idiosyncrasies or careless restaurant dietary habits to need inclusion in an overall survey such as this.

200 to 500 mg. cevitamic acid daily by mouth or parenterally will promptly correct the acquired reversible capillary permeability defect in such patients. Abnormal capillary permeability may be relieved also at times by vitamin P—hesperidin or hesperidin methyl chalcone,—in 50 mg. capsules, the total daily dose being 100 to 200 mg. usually combined with ascorbic acid.

*Mechanical Factors.* In hypertension and in the vascular congestion which follows myocardial decompensation the integrity of the capillary bed is always threatened and is frequently violated. When purpura occurs under such circumstances, selective supportive measures are required. The one major contraindication to blood transfusions is myocardial decompensation. The hypertensive and cardiac factors must therefore be brought under control by appropriate measures at the earliest possible moment.

The physiologic integrity of the capillaries must be maintained by every known means under these adverse circumstances. Vascular endothelial continuity must be guaranteed by an excess of vitamin C (200 to 500 mg. daily), and vitamin P (100 to 200 mg. daily). Rutin (flavonol glycoside extracted from buckwheat) in 20 to 30 mg. doses every four hours is said

to assist in decreasing capillary fragility in these patients, though its precise pharmacologic action has not been satisfactorily demonstrated. Optimum prompt coagulation of any extravasated blood must be assured through parenteral vitamin K therapy (4 to 10 mg. daily). Local or generalized hypoxia affects the functional integrity of endothelial cells as it does all other tissues and organs in the body, and when this danger of cell damage is added to the mechanical factors in congestive failure—oxygen therapy is urgently indicated, as it is in all other purpuras when a low oxygen tension in the tissues results from an excessive loss, or inadequate oxygenation, of the circulating hemoglobin.

*Anaphylactoid Purpura.* Purpura on the basis of an antigenic hypersensitization mechanism may occur: (1) secondary to specific megakaryocytic damage with a resultant thrombocytopenic purpura of central bone marrow origin; or (2) as the result of a generalized vascular endothelial sensitization, so-called "anaphylactoid purpura." A careful history, skin and dietary elimination tests for specific allergies may elicit one or more specific antigens which may then lead to avoidance or a specific desensitizing therapeutic regimen. More often than not, however, the antigenic specificity remains anonymous despite exhaustive testing.

When testing for a purpura producing antigen, a warning should be sounded relative to the extremely high degree of specific sensitization, which may develop in a patient to such drugs, for example, as Sedormid (see figure 5). In two instances in our own experience where this drug was suspected and an extremely small oral dose was repeated to establish it as the cause of a previous purpuric episode, a near fatal, generalized thrombocytopenic purpura was re-precipitated, lasting five to seven days, with widespread megakaryocyte damage. Forced fluids, to hasten elimination of the offending antigen, and supportive blood transfusions to supply platelets, are the treatment of choice and must be continued over the period required for megakaryocyte regeneration.

Lacking specific identification of the offending antigen, an autogenous urinary protease concentrate may be obtained from such patients, during periods of active anaphylactoid purpuric exacerbations and, when antigenic specificity is demonstrated, through intracutaneous skin testing, a therapeutic desensitizing regimen may be instituted, which will induce, in some patients, a most gratifying remission for an indefinite period, even for years.

The anti-histaminic drugs may at times be helpful; for example, Benadryl capsules, 50 mg., three to four times daily for adults, the elixir 10 mg. to the dram for children; Pyribenzamine, 50 mg. tablets, elixir 5 mg. per dram; Neo-antigan 50 mg. dosage two to four times daily.

Histamine in the form of the diphosphate may be employed as a non-specific desensitizing antigen: initial dosage 0.1 mg. subcutaneously, to be gradually increased at two to seven day intervals to 1 mg., or 2 mg. in 250 c.c. NaCl may be given, intravenously very slowly. The maintenance dose is 1 mg. once weekly.

High vitamins C and K are routinely indicated in every patient with anaphylactoid purpura. Hemorrhages from bowel and kidneys may at times require blood transfusion replacements.

*Embolic Petechiae in Sepsis.* Bacterial emboli produce a very specific type of readily identifiable petechial hemorrhage in skin and mucous membranes, in conjunctivae and nail beds, as, for example, in endocarditis lenta with the *Streptococcus viridans*. The toxemia of meningococcemia produces superficial ecchymoses and petechiae uniquely characteristic in type and distribution of an infectious agent. Isolation and identification of the specific organism and the prompt selection and administration of the appropriate chemo- or antibiotic therapeutic agent is the rational and only specific treatment for this type of purpura.

One of twin brothers, aged two years (figure 11) was admitted to the University Hospital with a generalized purpuric syndrome at about the same time and under circumstances similar to those already described for the patient with hypersplenic

0-9020 L.T.♂, AGED 2 YRS. One of twins, both showing acute infectious Thrombocytopenic Purpura within the same week.  
1 Acute Epidemic Gastroenteritis family and Community Wide (*Gram Negative Bacilli*)  
2 Pan-marrow Toxic Hypoplasia.  
3 Acute Thrombocytopenic Purpura.  
4 Blood Transfusions, Chemo and Antibiotic and Supportive Therapy.

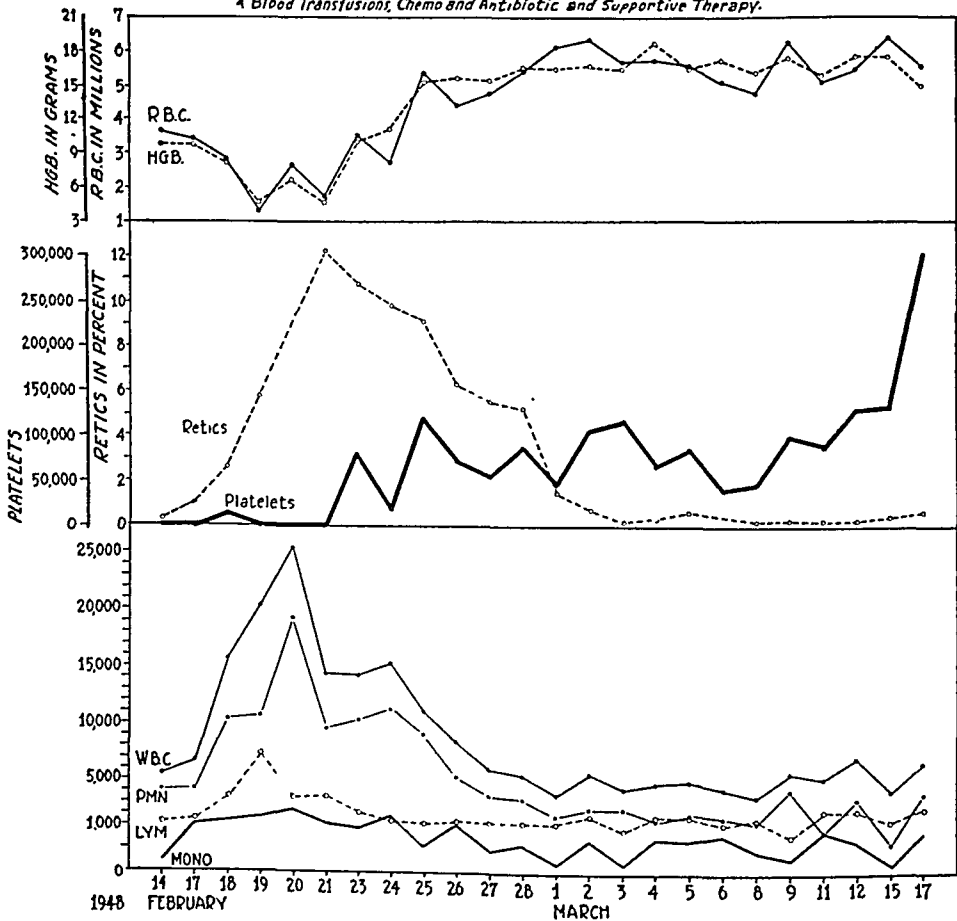


FIG. 11.

thrombocytopenia (figure 9). A non-hemorrhagic epidemic of enteritis, in community and home, had been communicated to the twins, each of whom promptly developed a marked bleeding diathesis with the infection. Again the circulating platelets were found to be extremely low or absent, but in this instance bone marrow studies revealed a central toxic picture affecting all cell types. The megakaryocytes were scarce and showed both nuclear and cytoplasmic degenerative vacuolization. Meticulous nursing care, supportive fresh whole blood transfusions and chemo- and antibiotic therapy resulted in the gradual regeneration of the essential marrow elements, followed by a return of platelets to the circulation with the permanent disappearance of all purpuric manifestations. Splenectomy under these circumstances would be fatal.

*Endocrine Deficiency.* Excessive uterine hemorrhage may occur as a part of any generalized purpuric syndrome in which platelet or plasma coagulation defects can be demonstrated, or it may present as a sometimes confusing, exsanguinating dysfunction, with minimal or no coagulation abnormalities, to be classified nevertheless as a "purpuric" manifestation. For immediate control, to arrest serious functional hyper- and polymenorrhea: (1) Ergotrate, grs. 1/320 every 4 to 12 hours, for not more than eight consecutive doses without 24 hr. rest period; (2) obstetrical pituitrin or pitocin, 1 ampoule, intramuscularly every 4 hrs., as long as necessary; (3) calcium gluconate or chloride, 10 c.c. 10 per cent solution intravenously. There is no incompatibility if the administration of all three of these agents is required in the same patient. For less urgent action effective within two to three days: testosterone 25 mg. per day; or antuitrin S, one or two ampoules daily; or stilbestrol, 5 to 10 mg. daily. A mild hypothyroid state is commonly associated with this syndrome and small doses of one-half to one gr. desiccated thyroid frequently are sufficient to readjust the responsible endocrine disequilibrium. Gynecologic consultation and examination are indicated when the hematologic coagulation mechanism has been eliminated as a precipitating or contributing factor in hypermenorrhea.

The informed physician and surgeon today may approach the patient with a hemorrhagic diathesis with a degree of assurance and confidence heretofore impossible, due to the increasing ease of quantitative evaluation and specificity of control of each individual factor in the complex physiologic mechanism of coagulation.

#### BIBLIOGRAPHY

- ALLEN, J. G., et al.: Abnormal bleeding, Jr. Am. Med. Assoc., 1949, cxxxix, 1251.  
 BRINKHOUS, K. M.: Clotting defect in hemophilia: deficiency in a plasma factor required for platelet utilization, Proc. Soc. Exper. Biol. and Med., 1947, lxvi, 117.  
 CONLEY, C. L., HARTMANN, R. C., and MORSE, W. I.: Clotting behavior of human platelet-free plasma: evidence for the existence of a "plasma thromboplastin," Jr. Clin. Invest., 1949, xxviii, 340.  
 DAVIDSON, C. S., EPSTEIN, R. D., MILLER, G. F., and TAYLOR, F. H. L.: Hemophilia: a clinical study of forty patients, Blood, 1949, iv, 97.  
 MACFARLANE, R. G., and BIGGS, R.: Fibrinolysis: its mechanism and significance, Blood, 1948, iii, 1167.  
 OWREN, P. A.: Coagulation of blood: investigations on a new clotting factor, Acta med. Scandinav., (Suppl. 194), 1947, cxxviii, 1-327.



- QUICK, A. J.: Components of the prothrombin complex, *Am. Jr. Physiol.*, 1947, cli, 63.
- QUICK, A. J., RENE, HONORATO C., and STEFANINI, MARIO: The value and the limitations of the coagulation time in the study of the hemorrhagic diseases, *Blood*, 1948, iii, 1120.
- QUICK, A. J., SHANHERGE, J. N., and STEFANINI, MARIO: The rôle of platelets in the coagulation of the blood, *Am. Jr. Med. Sci.*, 1949, ccxvii, 198.
- WARE, A. G., MURPHY, R. C., and SEEGER, W. H.: The function of Ac-globulin in blood clotting, *Science*, 1947, cvi, 618.
- WARE, A. G., and SEEGER, W. H.: Serum Ac-globulin: formation from plasma Ac-globulin: rôle in blood coagulation; partial purification; properties; and quantitative determination, *Am. Jr. Physiol.*, 1948, clii, 567.

# STUDIES ON THE MECHANISM OF CARDIAC INJURY IN EXPERIMENTAL HYPOTHERMIA \*

By KURT LANGE, M.D., DAVID WEINER, M.D., and MICHAEL M. A. GOLD, M.D., *New York, N. Y.*

THERE are numerous reports in the literature that subsequent to exposure to severe cold accompanied by a lowering of body temperature severe cardiac irregularities or sudden death may occur. These effects may occur even up to 24 hours after the exposure when the body temperature has long since returned to normal.<sup>1-6</sup> Such instances were encountered during the war with previous exposure to cold water (immersion) or with certain therapeutic uses of cold as an adjuvant in the treatment of malignancy. Numerous investigators have attempted to explain the hypothermic death but no single theory has found general acceptance.

Ariel, Bishop and Warren<sup>7</sup> report that in rabbits lowering of body temperature by immersion into cold water leads to a slowing of the heart rate with widening of the QRS complexes and marked prolongation of the S-T segments. Smith reports<sup>4</sup> similar observations in humans treated with cryotherapy and he states that death immediately after the therapy or within 24 hours is due to an anoxia caused by a decreased cardiac output. On autopsy of such patients who also had a marked reduction in respiratory rate neither the heart nor the cerebrum showed any remarkable changes. Clark<sup>8</sup> states that lowering of body temperature in the frog results in a reduction of heart rate, in a slowing of conduction, a decrease in force of contraction and a decrease in oxygen consumption. He states specifically that the rate is not a linear function of blood temperature in the rabbit or the frog. The most detailed data on the influence of lowered body temperature on the heart in humans are given by Kossmann<sup>5</sup> who noted the marked venous constriction which makes the taking of blood samples so difficult. He states that there is a linear relationship between body temperature and the length of the electrical systole as expressed by Bazett's formula. The T waves in his patients were markedly lowered with lowered body temperatures and the S-T segments became depressed. Auricular fibrillation was observed in four out of nine patients subjected to cryotherapy and Kossmann states that changes especially in the Q-T interval occurring in cooling may persist long beyond the lowering of body temperature. Tomaszewski<sup>6</sup> reports a case dying from exposure to cold in which the P-R interval and the intraventricular conduction time were

\* Received for publication December 16, 1948.

From the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals and the New York Medical College Research Unit (Metropolitan Hospital).

Carried out under a contract between the Research and Development Board of the Surgeon General, U. S. Army and the New York Medical College.

markedly prolonged and severe changes in the T waves had appeared; in spite of rewarming and an increase of pulse rate from 21 to 44 per minute the patient died. On autopsy no significant changes were discovered in the heart. Hook and Stormont<sup>9</sup> report progressive prolongations of P-R intervals and QRS complexes with cooling and bizarre changes in T wave patterns with deep inversions of T. They also attribute these changes to anoxemia due to slowing of respiration. Hamilton, Driebach and Hamilton<sup>10</sup> report a linear relationship between body temperature and heart rate and a general slowing of conduction with lowered temperatures in rats and kittens. They suggest that the cause for these changes is anoxemia induced by cold narcosis of the medullary centers. Crismon<sup>11</sup> describes that in experiments on rats the lowering of the body temperature is followed by a progressive slowing of the rate and prolongation of conduction, whereby the heart rate-temperature relation is linear. Blood pressure fell rapidly after an initial rise due to shivering and the author attributes death under such conditions to circulatory failure with subsequent regional asphyxia. Lutz and Werz<sup>12</sup> in contrast to all other observers draw the attention to the fact that with lowered body temperature the oxygen dissociation decreases and that this fact alone is theoretically able to explain death due to cold.

Our own experiments were stimulated by the observation that some animals, one limb of which was exposed to circulating cold water to produce trench foot, were unable to maintain their body temperature. They showed a gradual fall in temperature over a period of several days.<sup>13</sup> Electrocardiograms taken at regular intervals in such animals showed some outstanding changes. The rate became slower in a direct linear relation to their body temperature with the exception that in some of them there was an initial rise in pulse rate apparently due to shivering. Very soon, however, the linear relation was established with striking accuracy. The P-R intervals as well as the QRS complexes became progressively longer although the establishment of a direct mathematical relation is somewhat difficult due to the inherent errors in measuring such small intervals. In general, however, it may be said that in these prolonged exposures with slow reduction in body temperature the conduction slows proportionally to the reduction in body temperature (table 1, figure 1). The most significant changes, however,

TABLE I

Rabbit with One Leg Immersed in Running Water of 2°C. Loss of Body Temperature during 48 Hours and Changes in the Electrocardiographic Components

Body Temp., °C.	RR, sec.	Rate per min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
38.3	0.30	200	0.06	0.03	0.14	0.26
35.5	0.224	268	0.06	0.03	0.12	0.25
32.0	0.35	172	0.07	0.03	0.19	0.32
26.0	0.50	120	0.09	0.04	0.28	0.40

## RABBIT DURING TRENCHFOOT EXPOSURE

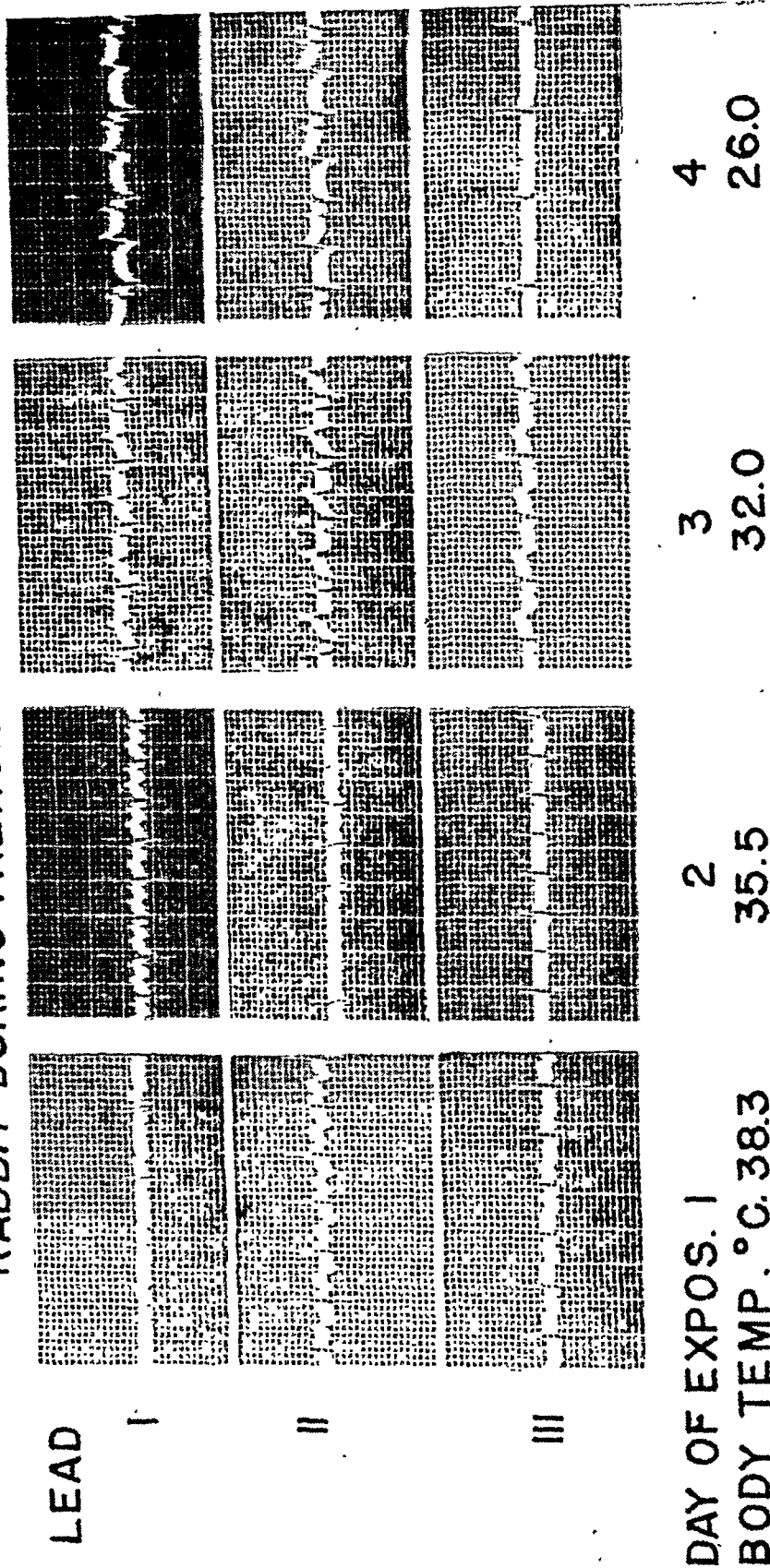


FIG. 1. Electrocardiograms of a rabbit during trenchfoot exposure with general loss of body temperature.

occur in the duration of electrical systole as determined by Bazett's formula  $QT/\sqrt{RR}$ . The systole becomes a progressively longer part of the cycle although the relation is not linear with body temperature as will be shown later. The T wave changes are most outspoken. From a lowering of T to a depression of the S-T segment to a sharp inversion of the T wave the changes move in a manner highly suggestive of progressive anoxia. At the same time the respiratory rate in such animals drops markedly although not in a linear relation to body temperature. In order to investigate these circulatory changes further, 28 clipped rabbits of four to six pounds body weight were exposed in a cold chamber to a temperature of  $-20^{\circ}\text{C}$ . frequently under pentothal sodium anesthesia to avoid electrocardiographic artefacts due to shivering. The survival time in such exposures is approximately two hours. In initial experiments it was demonstrated that this anesthesia in the dose given (1 to 1.5 c.c. nembutal per 5 pounds of body weight intraperitoneally) did not change the electrocardiogram during a similar period of observation when no cooling was used. The first group of animals was observed without artificial respiration and without anesthesia. They showed a constant relation between body temperature and respiratory rate which is shown in figure 2. The heart rate and the body temperature showed throughout the experiments a linear relationship as demonstrated in the example of one experiment in figure 3. This fact remained unaltered whether the animals were exposed with or without artificial respiration. The

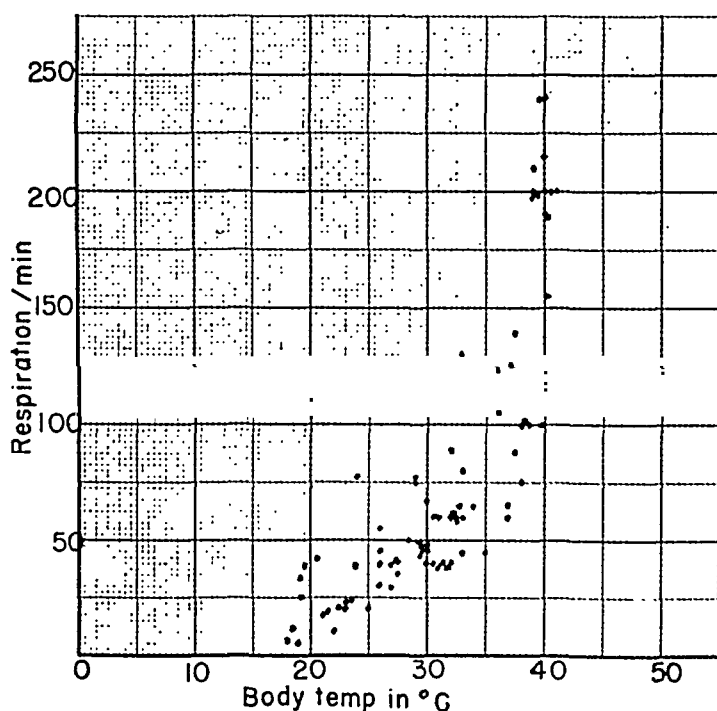


FIG. 2. Relation between respiratory rate and body temperature in 12 clipped rabbits exposed to an air temperature of  $-20^{\circ}\text{C}$ .

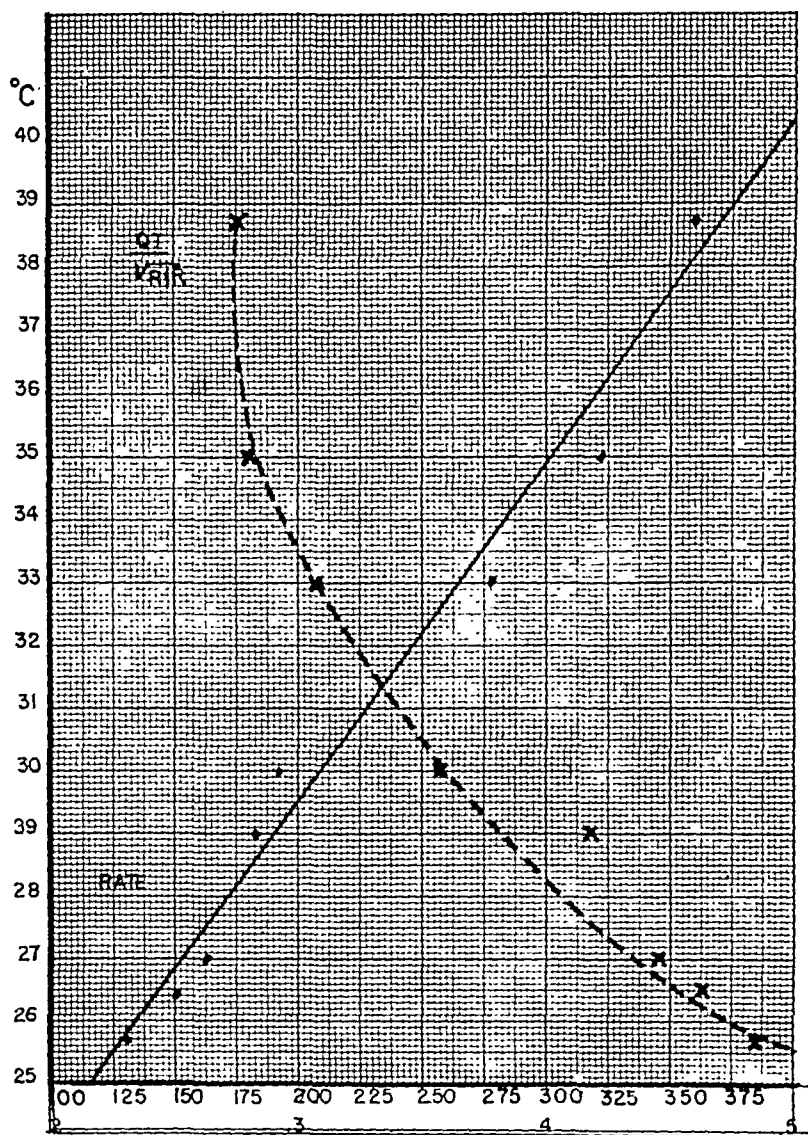


FIG. 3. Relation between body temperature, heart rate and electrical systole in a clipped rabbit exposed to an air temperature of  $-20^{\circ}\text{C}$ . Rewarming on electric heating pad.

slope of the curve permitted an exact prediction as to when heart standstill and death would occur and in those experiments which were carried to death under artificial respiration this prediction proved to be correct. The fact that artificial respiration at a constant rate did not influence the drop in heart rate proves that anoxemia does not have an influence on this relation. The P-R intervals and the QRS complexes became progressively longer in roughly a straight line relation to body temperature. The QT interval as evaluated by Bazett's formula showed changes which indicate a marked prolongation of systole during each cycle progressing with falling body temperature. The relation, although not linear, is a function of the temperature such that the systole is relatively more prolonged at lower temperatures (figure 3, table 2). These relations of prolongation of P-R

TABLE II

Clipped Rabbit under Pentothal Sodium Anesthesia Exposed to an Air Temperature of  $-20^{\circ}\text{C}$ . Rewarming on an Electric Heating Pad. Changes in the Electrocardiographic Components

Time (min.)	Body Temp., $^{\circ}\text{C}$ .	RR, sec.	Rate, min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
0	38.7	0.167	360	0.07	0.02	0.11	0.28
100 (cooling)	26.5	0.45	134	0.09	0.03	0.31	0.46
8 (heating)	25.7	0.47	129	0.11	0.04	0.33	0.49
20 (heating)	27.0	0.37	163	0.08	0.03	0.27	0.45
32 (heating)	29.0	0.39	155	0.08	0.03	0.26	0.42
40 (heating)	30.0	0.31	193	0.08	0.03	0.20	0.36
70 (heating)	33.0	0.22	277	0.07	0.02	0.15	0.30
78 (heating)	35.0	0.19	322	0.07	0.02	0.12	0.28

intervals, QRS complexes and electrical systole were not altered by the introduction of artificial respiration (table 3). This demonstrated that slowing of the respiratory rate is not a factor. Blood calcium levels taken in seven animals before and during the cooling remained unchanged indicating that hypocalcemia does not play a rôle in the prolongation of the Q-T interval. In contrast to the mathematical constancy observed in the P-R, QRS, QT, and rate changes, the T wave alterations varied in individual animals. The lead most affected was not always the same nor was the degree of abnormality constant. Lowering of the T waves, S-T segment depression, flattening and deep inversion were all observed. Again artificial respiration even with pure oxygen did not prevent or alter this indicating that these changes which give the distinct impression of being *anoxic* in nature are not due to an *anoxemia*. There was not a single animal that failed to show these T wave alterations to a considerable extent.

The anoxia may be due to a lowered oxygen dissociation. Barcroft and King were able to demonstrate that with lowering of body temperature the oxyhemoglobin dissociation decreases rapidly. The available oxygen at a tissue oxygen tension of 40 mm. Hg is, e.g., 27 per cent at  $36^{\circ}\text{C}$ . while

TABLE III

Clipped Rabbit under Pentothal Sodium Anesthesia and Artificial Respiration Exposed to an Air Temperature of  $-20^{\circ}\text{C}$ . Acid Sodium Phosphate Injected after Severe Lowering of Body Temperature

Body Temp., $^{\circ}\text{C}$ .	RR, sec.	Rate, per min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
35	0.25	240	0.06	0.02	0.15	0.30
27	0.53	113	0.09	0.03	0.32	0.44
23	0.90	67	0.11	0.04	0.52	0.55
22.5 (immediately after injection of 5 c.c. of 1N $\text{NaH}_2\text{PO}_4$ )	1.1	55	0.15	0.06	0.56	0.53
22.2 (2.5 minutes after injection)	0.88	68	0.13	0.06	0.50	0.53

at 20° C. it is only 3 per cent (figure 4). This means that although the hemoglobin is fully saturated with oxygen it is unable to release it to the tissue. We may then be dealing with an anoxia without anoxemia. It is interesting to note that poikilothermic animals have a much higher oxygen dissociation at low temperatures than homoiothermic animals thus enabling them to supply oxygen to their tissues even at low body temperatures.

The possibility occurred to us that Cytochrome C may be able to help the transfer of the oxygen from the hemoglobin to the tissue. Six animals were therefore given 2 to 4 c.c. of Cytochrome C (Wyeth) after they were cooled to a body temperature of approximately 25° C. The electrocardiographic changes were not in the least improved by this treatment.

#### OXYGEN DISSOCIATION CURVES FOR HUMAN BLOOD

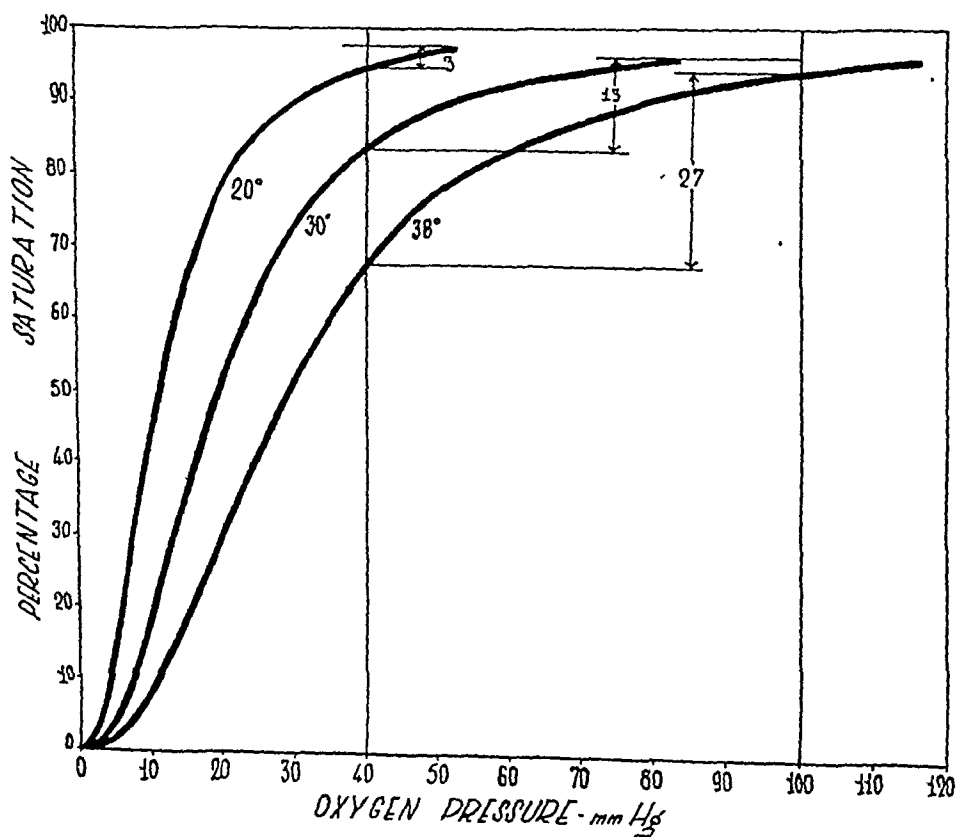


FIG. 4. Oxyhemoglobin dissociation curves for human blood at various temperatures.

We attempted to compensate for the lowered oxygen dissociation by increasing the amount of oxygen physically dissolved in the plasma independent of the hemoglobin. We calculated that this would require a 25 fold increase in the partial pressure of oxygen in the inspired air. This was accomplished by placing a severely cooled rabbit in a compression chamber containing 100 per cent oxygen at a pressure of 75 pounds per square inch.



Within seven minutes the abnormal electrocardiogram had improved markedly and on subsequent decompression to a normal atmosphere the anoxic pattern reappeared (figures 5 and 6).

Since acidification of the blood is known to produce an increased oxygen dissociation, i.e., to act just in the opposite direction of reduction of temperature, an attempt was made to acidify the blood of animals when they

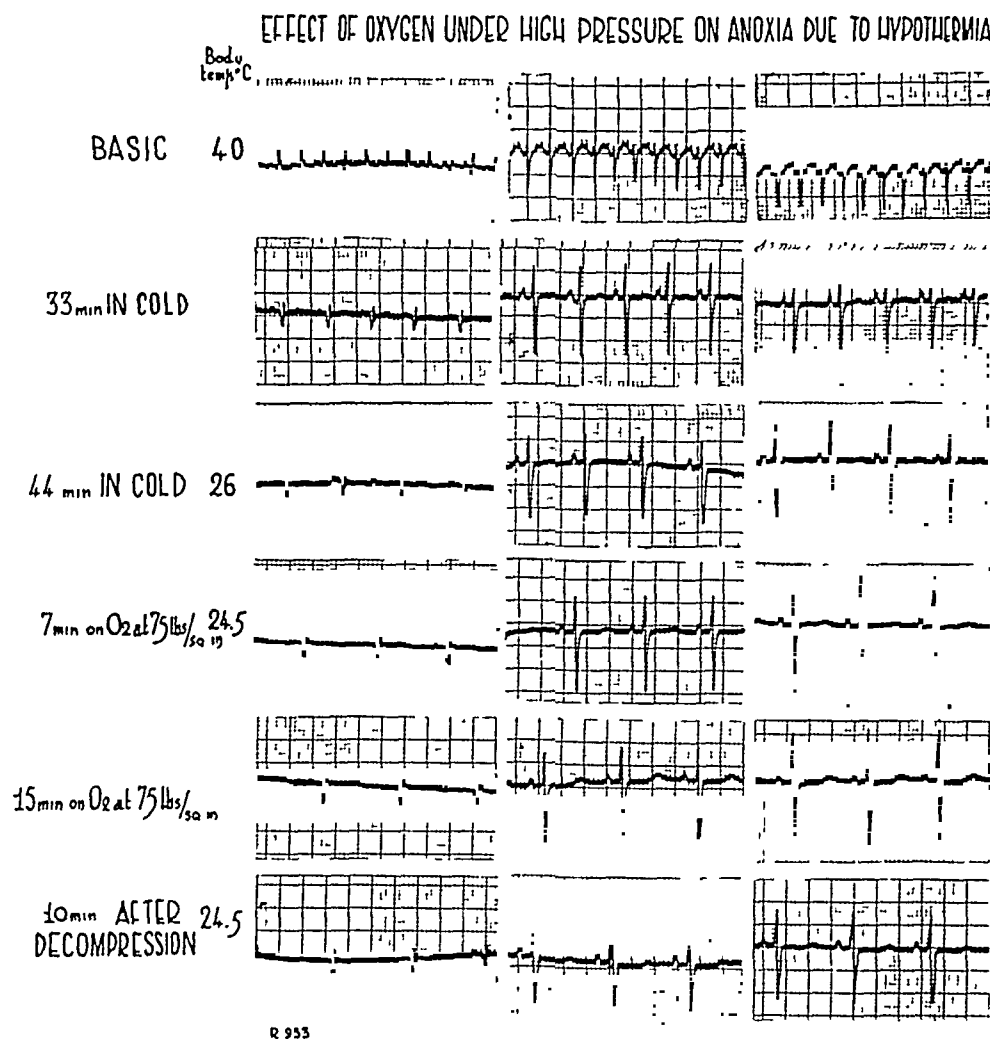


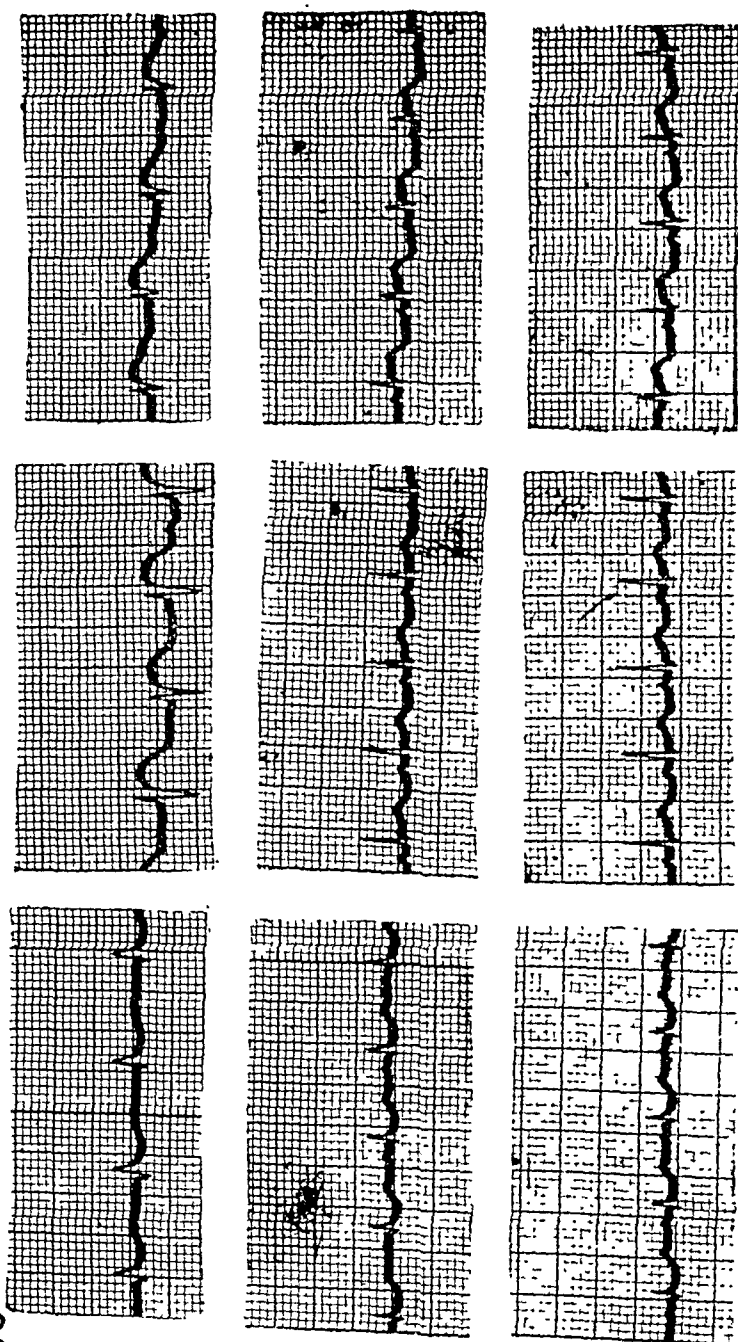
FIG. 5. Electrocardiograms (limb leads) of a rabbit before and after hypothermia and before and after exposure to an atmosphere of 100 per cent oxygen under a pressure of 75 lbs. per sq. inch.

showed the severe T wave changes at low body temperatures. Five to 10 c.c. of acid sodium phosphate ( $\text{NaH}_2\text{PO}_4$ ) in .5 or 1 N concentration were injected intravenously in 11 rabbits. Seven of these animals were examined with artificial respiration. In all of them the injection caused an immediate short lasting but very clear-cut return of the T waves to or towards normal (figures 7 and 8). The injection also caused a short-lived hyperpnea in

## EFFECT OF OXYGEN UNDER HIGH PRESSURE ON ANOXIA DUE TO HYPOTHERMIA

Body temp. °C

COOLED TO 28

4 min in PRESSURE  
CHAMBER AT 76 lbs./sq. in.6 min in PRESSURE 27.5  
CHAMBER AT 76 lbs./sq. in.

R 836

FIG. 6. Electrocardiograms (limb leads) of a rabbit after hypothermia and before and after exposure to an atmosphere of 100 per cent oxygen under a pressure of 75 lbs. per sq. inch.

those animals which were not under artificial respiration, so that the objection could be raised that the improvement was due to respiratory relief of anoxemia. Such an objection is not valid, however, in the seven animals which were under artificial respiration. Here the influence of the acidification by  $\text{NaH}_2\text{PO}_4$  alone must be considered the cause of the reversal of the

# INFLUENCE OF $\text{NaH}_2\text{PO}_4$ ON THE EKG OF A COOLED RABBIT (ART. RESPIRATION)

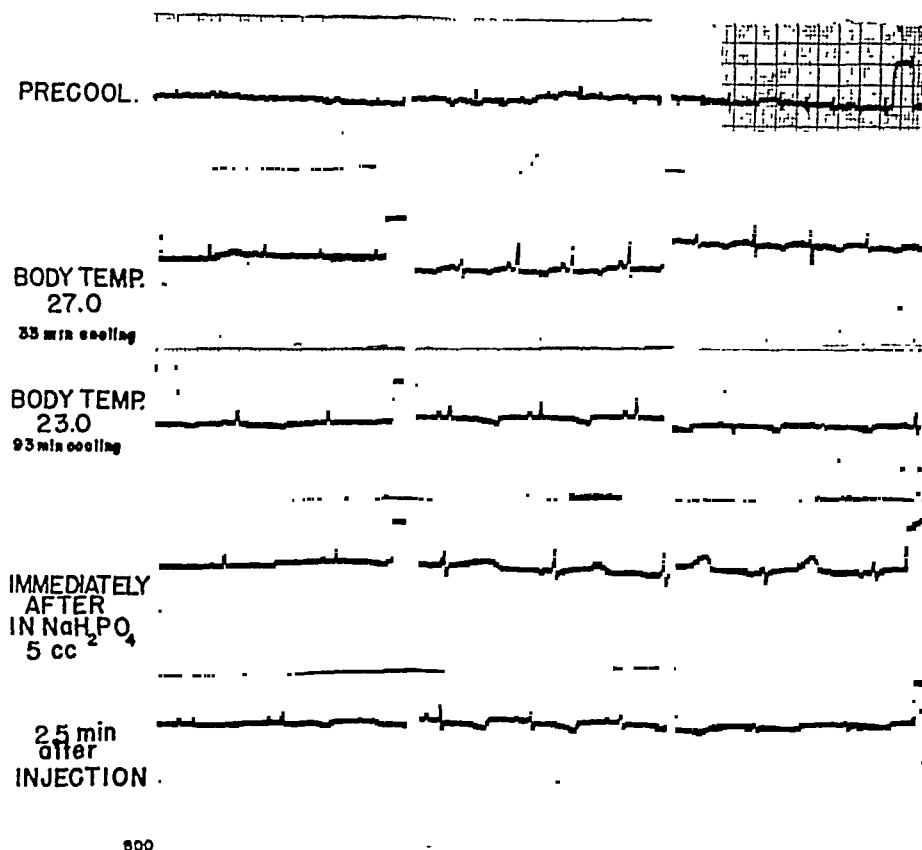


FIG. 7. Electrocardiograms of a clipped, anesthetized rabbit under artificial respiration exposed to an air temperature of  $-20^{\circ}\text{C}$ . After a severe hypothermia  $\text{NaH}_2\text{PO}_4$  is injected.

T waves towards normal. At the same time the injection produces a further slowing of the rate and a further prolongation of the P-R interval. The relative length of the electrical systole, however, is shortened by the acidification (table 3 and 4). Similar results can be obtained by injecting 1/10 N hydrochloric acid or by administering 20 per cent gluconic acid. That the injection of  $\text{NaH}_2\text{PO}_4$  alone in a normal uncooled anesthetized animal under artificial respiration does not produce any T wave or other electrocardiographic changes was shown in two animals (table 5).

Measurements of the pH of the arterial blood of such animals before and after the intravenous injection of acids revealed a lowering of the pH by 0.2 to 0.9 in individual experiments.

# EFFECT OF ACIDIFICATION ON ANOXIA DUE TO COLD (ART. RESPIRATION, PENTOBARBITAL SODIUM)

Rectal  
temp. °C Blood pH

BASIC

BEFORE COOLING 39 7.47

AFTER COOLING 25.5 7.49

3 min. oxy infusion of

10% GLUCONIC ACID 25 6.89

8 min. oxy infusion of

10% GLUCONIC ACID 25 7.05

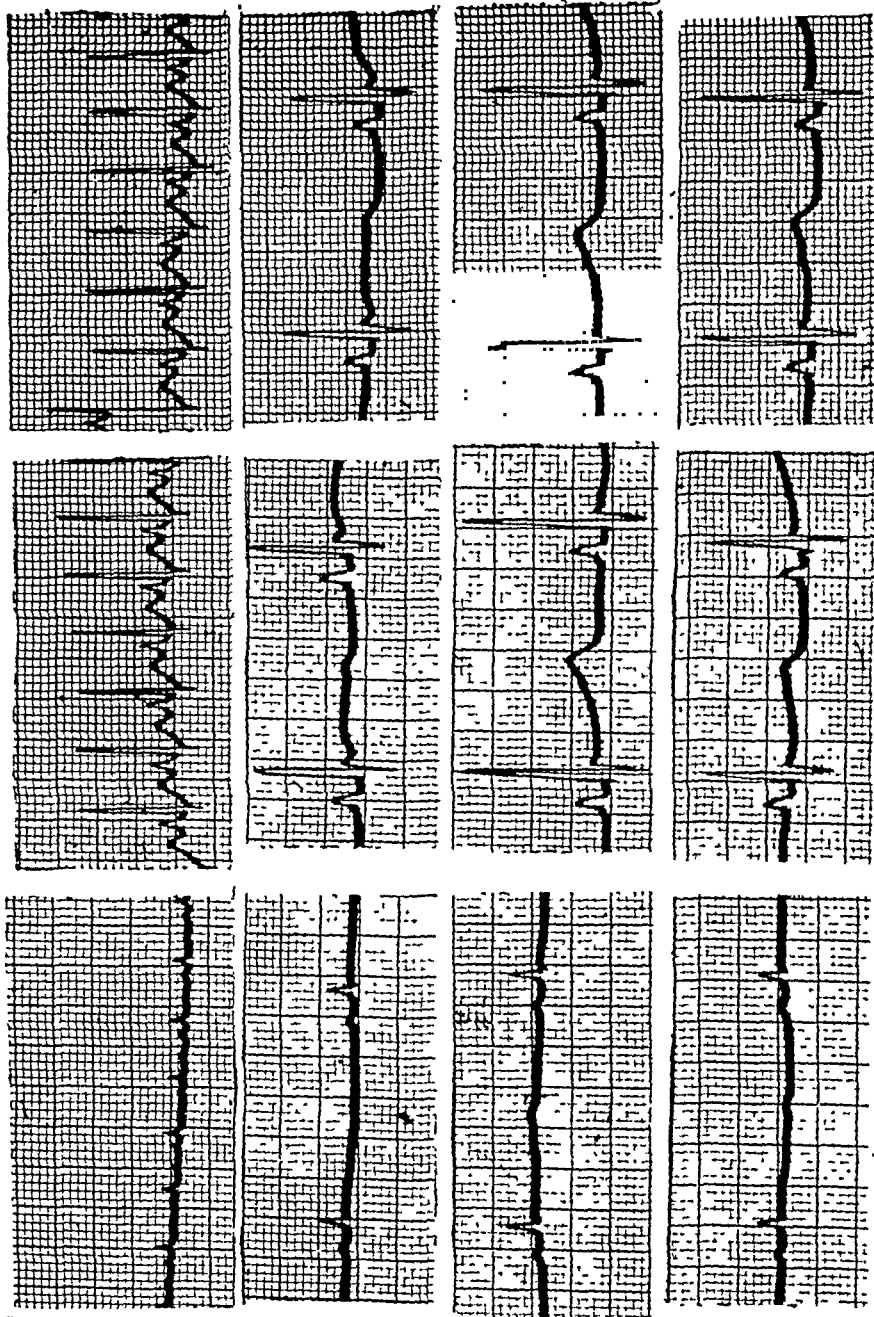


FIG. 8. Electrocardiograms of a clipped, anesthetized rabbit under artificial respiration exposed to an air temperature of  $-20^{\circ}\text{C}$ . After a severe hypothermia  $\text{NaH}_2\text{PO}_4$  is injected.

TABLE IV

Clipped Rabbit under Pentothal Sodium Anesthesia and Artificial Respiration Exposed to an Air Temperature of  $-20^{\circ}\text{C}$ . Acid Sodium Phosphate Injected after Severe Lowering of Body Temperature

Body Temp., $^{\circ}\text{C}$ .	RR, sec.	Rate, per min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
36	0.31	193	0.08	0.02	0.20	0.36
24.6	0.69	81	0.10	0.04	0.46	0.55
24 (immediately after injection of 5 c.c. of 1N $\text{NaH}_2\text{PO}_4$ )	0.85	71	0.12	0.04	0.48	0.52
24 (4 minutes after injection)	0.87	69	0.12	0.04	0.48	0.515

TABLE V

Influence of an Injection of Acid Sodium Phosphate on an Anesthetized Clipped, not Cooled Rabbit

Time	RR, sec.	Rate, per min.	PR, sec.	QRS, sec.	QT, sec.	$\frac{QT}{\sqrt{RR}}$
Before injection	0.24	250	0.07	0.02	0.15	0.31
30 seconds after injection of 5 c.c. of 1N $\text{NaH}_2\text{PO}_4$	0.27	222	0.07	0.03	0.15	0.29
90 seconds after injection	0.25	240	0.07	0.03	0.15	0.30
2.5 minutes after injection	0.25	240	0.07	0.02	0.15	0.30
6 minutes after injection	0.27	222	0.07	0.02	0.16	0.31

Experiments in dogs, which will be reported separately, revealed identical EKG changes and pH deviations.

### CONCLUSIONS

From these experiments it is evident that lowering of body temperature in rabbits is accompanied by a proportional fall in pulse rate which permits an exact prediction of the temperature at which heart-standstill will occur. This relation in rate is not due to anoxemia and not improved by availability of oxygen by means of acidification of the blood. Thus it is dependent only on the direct effect of the cold on the pacemaker or its governors. The relationship to temperature also holds true for the changes occurring in the P-R interval and the QRS complex. They too seem to be directly and exclusively dependent on the effect of the temperature on the specific conduction system. Anoxemia and relief of anoxia do not influence these factors. The length of systole increases markedly but not in linear relation with cold. It is to a larger extent produced by a direct influence of the lowered temperature on the muscle. To a certain extent, however, anoxia favors this extension of systole in the cycle. With relief of anoxia the length of systole is shortened, i.e., the sluggishness of the muscular contraction is improved. The T wave changes seen in cold are entirely the result of

anoxia for they can be completely reversed by making oxygen available through acidification of the blood with subsequent improvement of the oxygen dissociation or by increasing the amount of oxygen physically dissolved in the plasma. It is therefore possible that the reported deaths subsequent to severe exposure to cold are due to longstanding anoxic damage of the heart muscle too early to be detected by present morphologic methods.

In patients recovering from hypothermia it may therefore be advisable to treat them for a short period of time as if they had myocardial infarctions.

### SUMMARY

1. The literature on the influence of hypothermia on cardiac rate, conduction and the myocardium is reviewed.

2. Rabbits suffering from slow or rapid lowering of body temperature show a reduction in heart rate directly proportional to the fall of body temperature.

3. The P-R interval and the QRS complex are also roughly proportional in their prolongation to the fall in body temperature.

4. The relative prolongation of electrical systole is not a linear function of body temperature. It becomes relatively more prolonged at lower body temperatures.

5. The very marked changes in the S-T segment and the T wave under such conditions show individual differences in extent and localization.

6. The changes in rate and conduction are exclusively the result of the direct effect of cold. The prolongation of electrical systole is partly the result of cold directly on the muscle fibers and partly the result of anoxia due to lowered oxygen dissociation. The T wave changes are exclusively the result of anoxia.

7. The anoxic nature of the S-T segment and T wave changes as well as part of the prolongation of electrical systole is proved by the fact that increasing the oxygen dissociation of the blood by acidification reverses them to normal. Increasing the amount of oxygen physically dissolved in the plasma also reverses these changes.

8. Acidification of the blood does not change the electrocardiogram of uncooled rabbits.

9. Anoxemia plays no rôle in the production of any of the changes seen in the heart with exposure to cold. We are dealing with anoxia without anoxemia.

### BIBLIOGRAPHY

1. WAYBURN, E.: Immersion hypothermia, *Arch. Int. Med.*, 1947, lxxix, 77.
2. UNGLEY, C. C.: Research and development of life saving equipment. Medical aspects of shipwreck. British Intelligence Objectives Sub-Committee Final Report No. 494, Item No. 24.
3. ALEXANDER, L.: The treatment of shock from prolonged exposure to cold, especially in water. Combined Intelligence Objectives Sub-Committee.
4. SMITH, L. W.: The use of cold in medicine, *Ann. Int. Med.*, 1942, xvii, 618.

5. KOSSMANN, E.: General cryotherapy. A Symposium. Cardiovascular aspects, Bull. N. Y. Acad. Med., 1940, xvi, 317.
6. TOMASZEWSKI, W.: Changements electrocardiographiques observés chez un homme mort de froid, Arch. de mal de froid, 1938, xxxi, 525.
7. ARIEL, J., BISHOP, F. W., and WARREN, S. L.: Studies on the effect of hypothermia. Acute physical and physiological changes induced by the prolonged hypothermic state in the rabbit, Cancer Res., 1943, iii, 448.
8. CLARK, A. I.: The effect of alterations of temperature upon the functions of the isolated heart, Jr. Physiol., 1920, liv, 275.
9. HOOK, W. E., and STORMONT, R. T.: Effect of lowered body temperature on heart rate, blood pressure and electrocardiogram, Am. Jr. Physiol., 1941, cxxxiii, 334.
10. HAMILTON, J. B., DRIEBACH, M., and HAMILTON, R. S.: Cardiac changes during progressive hypothermia, Am. Jr. Physiol., 1937, cxviii, 71.
11. CRISMON, J. M.: Effect of hypothermia on the heart rate, the arterial pressure and the electrocardiogram of the rat, Arch. Int. Med., 1944, lxxiv, 235.
12. LUTZ, W., and WERZ, R. V.: Kältetod and Sauerstoffmangel, quoted from, The treatment of shock from prolonged exposure to cold, especially in water. Combined Intelligence Objectives, Sub-Committee.
13. LANGE, K., WEINER, D., and BOYD, L. J.: The functional pathology of experimental immersion foot, Am. Heart Jr., 1948, xxxv, 238.

# CORONARY OCCLUSION AND MYOCARDIAL INFARCTION ASSOCIATED WITH CHRONIC RHEUMATIC HEART DISEASE\*

By FRANCES E. GARDNER, *London, England*, and PAUL D. WHITE, *F.A.C.P., Boston, Massachusetts*

ALTHOUGH isolated cases have been reported (Kerr et al., 1925; Breiten-ecker, 1931), coronary artery obstruction has long been regarded as an uncommon complication in rheumatic heart disease. White and Jones (1928) found only one patient who had suffered a coronary thrombosis in 956 cases of rheumatic endocarditis. Among 99 patients dying with pure aortic stenosis Contratto and Levine (1937) reported four instances of coronary occlusion, and in 314 consecutive cases of simple mitral stenosis (Levine and Kauvar, 1941) coronary occlusion was diagnosed in only 10 instances (confirmed at autopsy in five). Rheumatic heart disease is found in less percentage still among patients with coronary heart disease. Only recently Cassidy (1946) reported that in 2000 cases of coronary heart disease he has not seen a single instance of concomitant chronic rheumatic endocarditis.

There seems no a priori reason why middle-aged and elderly patients with rheumatic heart disease should not develop coronary artery atherosclerosis as frequently as others without rheumatic stigmata. Indeed, since right and left ventricular hypertrophy commonly follow rheumatic valvular lesions, it might even be supposed that the latter condition would predispose to coronary insufficiency. Moreover, if, as Zeek (1932) and Karsner (1934) have claimed, acute rheumatic fever is attended by widespread lesions of the coronary arteries and predisposes to precocious coronary sclerosis, it might be assumed that patients with rheumatic heart disease would be unduly liable to coronary thrombosis and that this liability would become apparent at an earlier age than is usual in uncomplicated degenerative coronary disease. The reported figures suggest that coronary occlusion is infrequent in rheumatic heart disease; it is noteworthy, however, that with the exception of Levine's and Kauvar's five autopsied cases the figures are based on clinical diagnoses alone.

It is our belief that, in the absence of signs of gross valvular lesions, the presence of rheumatic heart disease may be overlooked in elderly patients and hence the real frequency of the association of this condition with coronary heart disease, if based on clinical records alone, may be underestimated. We have, therefore, made a study of necropsy material and compared the results with our more recent clinical records in order to check any discrepancy in our clinical findings. We also hoped to obtain a clearer picture of the relationship, if any, between rheumatic and coronary heart disease.

\* Received for publication June 3, 1948.



## MATERIAL. I. NECROPSY SERIES

In 6,000 consecutive autopsies at the Massachusetts General Hospital there were 436 patients dying with rheumatic heart disease and 513 patients dying with coronary heart disease.\* Thirty-two patients were found to have both rheumatic and coronary heart disease. Thus, in this series, about 7 per cent of patients with rheumatic heart disease also suffered from coronary heart disease, and about 6 per cent of patients with the latter condition had accompanying rheumatic endocarditis.

*Clinical Findings.* In this group of 32 patients with rheumatic and coronary heart disease, 15 were male and 17 female, and their ages ranged from 42 to 82 years, with the greatest incidence in the sixth and seventh decades. Nine patients had a history of acute rheumatic fever and/or rheumatic heart disease, and angina pectoris. Seven had a history of rheumatism alone, eight of angina pectoris alone, and eight patients had nothing in their histories to suggest either condition. Five of the 32 patients had a history of old myocardial infarction.

Relevant physical findings, aside from the signs of valvular disease, were hypertension in 13 patients and arrhythmias in 16.

Auricular fibrillation was present in 14 patients. Nine of these were under observation for months or years. Auricular fibrillation started in one patient after a posterior myocardial infarct nine months before death, and two patients, known to have had rheumatic heart disease, had auricular fibrillation for seven months and four years respectively before death. In the six remaining cases the onset of auricular fibrillation was terminal. Five patients were seen only during the final illness when auricular fibrillation was present throughout the period of observation.

Complete auriculoventricular block was found in one patient. This was a man of 57 who died as a result of myocardial infarction. The heart block was known to have been present for at least two years.

Paroxysmal tachycardia was present in one patient who was under observation for only four weeks before death.

*Electrocardiograms* (standard leads and in a few instances  $CF_4$ ) of 25 patients were relevant in relation to the coronary accident so far as could be judged from the autopsy specimens. In 21 cases of myocardial infarction 11 records showed changes characteristic of this condition and six were suggestive. In the four cases with coronary occlusion without infarction, one electrocardiogram showed evidence of myocardial changes, two showed auricular fibrillation and digitalis effects, and the fourth, from a patient with known mitral and aortic valve disease, showed left bundle branch block.

*Pathological Findings.* Autopsy examination revealed rheumatic lesions of both mitral and aortic valves in 23 of the 32 hearts; the aortic valves were

\* For the purpose of this study the designation "coronary heart disease" was limited to cases in which there was either myocardial infarction or coronary occlusion without infarction.

affected alone in five hearts and the mitral valves alone in four. Mitral stenosis was judged to be present in 13 cases and aortic stenosis in eight. Using White's criteria (1944) for the measurements of the valve circumferences we would consider only seven patients to have had clinically important mitral stenosis, that is, a circumference of the mitral orifice of less than 7.5 cm., and in no case was the aortic ring less than 5 cm. in circumference. Myocardial infarction was found in 25 hearts. In 12 the infarcts were recent, in eight they were of long standing, and in five there were both old and recent infarctions. In all but three cases the left ventricle bore the brunt of the infarctive process and anterior wall infarctions (19) were found with slightly greater frequency than posterior (15). Widespread atherosclerotic disease of the coronary arteries was found in all but one instance. In eight hearts no actual occlusion of the coronary artery could be demonstrated, but in nine two or more large vessels were thrombosed.

*Correlation of Clinical with Pathological Findings.* A correct antemortem diagnosis of combined rheumatic and coronary heart disease was made in only seven of the 32 patients. Coronary heart disease alone was diagnosed in 20 cases, rheumatic heart disease alone in four, and in one patient who died of a cerebral accident after a vaginal hysterectomy neither condition had been suspected during life. In only five cases was there failure to recognize the coronary heart disease, though in 10 the presence of recent myocardial infarction was unsuspected. Rheumatic heart disease was unrecognized in 21 of the 32 patients, and mitral stenosis was missed in three of the seven patients where definite postmortem evidence of considerable stenosis was present.

TABLE I

Showing (I) Age and Sex Distribution of Patients Dying with Uncomplicated Coronary Heart Disease, Uncomplicated Rheumatic Heart Disease, and Combined Rheumatic and Coronary Heart Disease in 6,000 Consecutive Autopsies at the M. G. H. and (II) Age and Sex Distribution in 57 Patients with Combined Rheumatic and Coronary Heart Disease in 10,000 Consecutive Cases Seen in the Private Practice of P. D. W.

Age	I Necropsy Series									II Clinical Series
	Uncomplicated Coronary Heart Disease			Uncomplicated Rheumatic Heart Disease			Rheumatic and Coronary Heart Disease			Rheumatic and Coronary Heart Disease
	All	M	F	All	M	F	All	M	F	
Under 40	11	10	1	122	61	61	0	0	0	0
40-49	34	30	4	69	36	33	2	2	0	2
50-59	115	90	25	88	49	39	12	6	6	30
60-69	179	128	51	75	45	30	13	5	8	16
70-79	119	79	40	41	24	17	2	0	2	9
80-89	23	13	10	9	5	4	3	2	1	0
Total 40 years and over	470	340	130	282	159	123	32	15	17	(M 40; F 17) 57

It should be noted that these patients were admitted on medical, surgical, and gynecological services, and although the cardiological group were able to examine some of them others were under the care of physicians or surgeons more directly interested in other fields.

*Sex and Age Incidence of Coronary and Rheumatic Heart Disease in the Autopsy Series.* The table shows the sex and age distribution of all patients dying with uncomplicated coronary heart disease, uncomplicated rheumatic heart disease, and coronary and rheumatic heart disease combined among the 6,000 autopsies.

It can be seen that there were 282 persons of 40 years and upwards dying of rheumatic heart disease, 123 of whom were females. There were 470 persons in the same age group dying with uncomplicated coronary heart disease, and only 130 of these were women. Among the patients with combined lesions there was no instance of coronary occlusion or myocardial infarction under the age of 40, and the highest incidence of this combination occurred in the sixth and seventh decades, roughly corresponding to the incidence for the cases of uncomplicated coronary heart disease.

## II. CLINICAL SERIES

We have examined the records of 10,000 cardiovascular cases seen in the consulting practice of one of us (P. D. W.) to discover how frequently the diagnosis of combined rheumatic and coronary heart disease has been made. Among the 10,000 cases there were 2,840 instances of coronary heart disease, 1,346 of rheumatic heart disease, and only 57 patients (40 men and 17 women) where both conditions could be diagnosed with certainty. In this series, therefore, only 2.0 per cent of patients with coronary heart disease had clinically recognizable rheumatic heart disease, in contrast to the 6 per cent found in our autopsy series. On the other hand, 4.2 per cent of the patients with rheumatic heart disease had a diagnosis of accompanying coronary heart disease, a proportion corresponding more closely with our autopsy findings.

The difficulty of making the dual diagnosis may be illustrated by the following patient who has been under observation for the past 10 years.

Mrs. H. G., aged 68, first consulted us in 1937 for breathlessness on exertion and general fatigue. She gave a history of rheumatic fever at the age of 12 and again at 49 and of high blood pressure for a few years. Cardiological examination in 1937 showed a slightly enlarged heart with regular rhythm, normal heart sounds, and a slight aortic systolic murmur; blood pressure 170 mm. Hg systolic and 100 mm. diastolic. In February 1942 she had an acute myocardial infarction confirmed by characteristic electrocardiographic changes. She made a fairly satisfactory recovery, but for the next 18 months she complained of fatigue and suffered recurrent bouts of moderate left ventricular failure. In September 1943 she was in fair health again but on examination Grade III systolic and Grade I diastolic murmurs were audible for the first time in the aortic area. At subsequent examinations only a moderate aortic systolic murmur and no diastolic murmur was heard. She continued to have mild left ventricular failure until she was admitted to the hospital in June 1945 for surgical treatment of carcinoma of the rectum. At this time the aortic systolic and diastolic murmurs were again heard, and in addition there was a Grade I mitral

diastolic murmur with definite presystolic accentuation, and the diagnosis of rheumatic heart disease with slight aortic stenosis and regurgitation and slight mitral stenosis was made. Since that time the same murmurs have invariably been present, though often very careful auscultation has been necessary to detect them.

We now think it possible that a recurrent smoldering rheumatic carditis may have been partially responsible for the periods of ill health and left ventricular failure to which this patient was subject, but the hypertension and the myocardial infarction had been thought to be sufficient explanation for her condition until unequivocal evidence of valvular disease appeared. Had this complication been in mind, it is possible that a more diligent search might have revealed characteristic murmurs at an earlier date.

### DISCUSSION

The small number of cases with completely accurate antemortem diagnosis in our autopsy series demands comment. That rheumatic heart disease was unrecognized in as many as 21 of 32 cases suggests a low index of clinical suspicion. It is true that only in seven instances was there any considerable stenosis of the mitral valve, but three of these were unrecognized during life. It is also true that several patients were moribund when first examined and any signs of valvular disease which may have been present were obscured by tachycardia, gallop rhythm, or pulmonary edema consequent upon acute myocardial infarction, but in these, so far as we know, the diagnosis of rheumatic heart disease had not been made prior to their coronary illness. Moreover, it may be difficult to diagnose rheumatic heart disease with certainty in elderly patients. A history of rheumatic fever in youth is frequently lacking; it was obtained in only five of the undiagnosed cases. The presence of auricular fibrillation is of little assistance, for in this age group this arrhythmia may be due to a number of causes other than rheumatic heart disease with mitral stenosis. In our series it was found in only three of the patients with unsuspected rheumatic heart disease where adequate observation was possible during life, and in these either coronary or hypertensive heart disease was thought to be sufficient explanation. Nevertheless, there is a certain unawareness of the possibility of combined rheumatic and coronary heart disease. In several instances the significance of basal and apical systolic murmurs was underestimated, and in three patients although aortic valve disease was recognized during life it was attributed to atherosclerotic changes rather than to rheumatic heart disease.

Although the numbers in our autopsy and clinical series are small, it is clear that we are still overlooking chronic rheumatic endocarditis among patients with coronary heart disease, for in the clinical series only 2.0 per cent of the patients with the latter condition had recognized rheumatic heart disease in contrast to the 6 per cent in the autopsy series. It might be questioned whether or not unrecognized rheumatic heart disease has any significance in patients under observation for coronary insufficiency. Certainly unrecognized recent myocardial infarction has more serious conse-

quences than unsuspected rheumatic heart disease, but smoldering rheumatic infection, even in elderly patients, may account for ill health and serious sequelae. This is illustrated by a patient with hypertensive and coronary heart disease recently seen by one of us (P. D. W.) where the sudden onset of auricular flutter precipitated acute pulmonary edema and the underlying rheumatic heart disease was only discovered after a careful search revealed the murmur of mitral stenosis. We can offer no easy way by which the diagnosis of rheumatic heart disease can be made in 100 per cent of cases. Electrocardiographic and roentgenological findings are, as a rule, not helpful; the rhythm is usually normal, right axis deviation is uncommon, and the left auricle is often not appreciably enlarged. We can only urge a more diligent search for the characteristic murmurs which are the hallmark of the condition.

An interesting feature of this investigation is the high proportion of female patients in the autopsy series with both rheumatic and coronary heart disease. That it is not due to a preponderance of women dying with rheumatic heart disease in these particular age groups, or to an unusual sex distribution in our series of patients dying with coronary heart disease, is shown in the table. Of the 282 persons 40 years of age and upwards dying with rheumatic heart disease, less than one half were female. Moreover, of the 470 persons in the same age group dying with uncomplicated coronary heart disease, less than one third were women. This sex distribution corresponds with the figures usually reported in large series of patients dying with these diseases. We are unable to offer any satisfactory explanation for the fact that over 50 per cent of the patients with both coronary and rheumatic heart disease in the autopsy series were women; the smallness of this group, only 32 in all, may be the answer. In our clinical series men outnumbered the women more than two to one. The discrepancy between the two groups might perhaps be explained by our failure to detect the presence of rheumatic heart disease in a number of women with coronary artery degeneration.

The frequency with which aortic valve disease was found at autopsy is noteworthy. Fourteen of the 15 men (93 per cent) and 14 of the 17 women (82 per cent) had lesions of the aortic valves. In 282 persons in the same age group dying with uncomplicated rheumatic heart disease, only 75 per cent of the men and 60 per cent of the women had aortic valvulitis. It is impossible to draw conclusions from such a small group of cases, but these facts suggest the possibility that patients over the age of 40 with rheumatic heart disease are more likely to develop serious coronary artery degeneration if the rheumatic lesion implicates the aortic valves.

It is clear from the table that this study provides no evidence in support of Karsner's view that rheumatic heart disease predisposes to premature coronary artery degeneration. In neither the autopsy nor the clinical series was there a single case of combined rheumatic and coronary heart disease under 40 years of age. We can only conclude that the presence of rheumatic heart disease has no direct influence on the incidence of degenerative disease of the coronary arteries.

## SUMMARY

1. In 6,000 consecutive autopsies there were 436 cases of rheumatic heart disease and 513 cases of coronary heart disease, 32 of which had both conditions (7 per cent of the rheumatics and 6 per cent of the coronary cases). Fifteen were male and 17 female.

2. In 10,000 consecutive clinical cases 1,346 were diagnosed as having rheumatic heart disease and 2,840 coronary heart disease, 57 of which had both conditions (4.2 per cent of the rheumatics and 2.0 per cent of the coronary cases). Forty were men, and 17 were women.

3. Aortic valve disease was found in 28 of the 32 fatal cases of combined coronary and rheumatic heart disease (87 per cent). It was present in only 69 per cent of the fatal cases of uncomplicated rheumatic heart disease. Mitral valve disease was found in 27 of the 32 (84 per cent).

4. A completely correct antemortem diagnosis was made in only seven of the 32 cases, although either rheumatic or coronary heart disease was diagnosed in 31 of the cases. The rheumatic heart disease was overlooked in 21 of the 32 patients.

5. Incomplete diagnosis was to some extent inevitable because of the moribund state of some of the patients when examined. To some extent it was probably also due to a common clinical unawareness that coronary and rheumatic heart disease may be associated.

6. The relatively low incidence of rheumatic heart disease among the coronary cases in the clinical series suggests that the former condition is still being overlooked in these patients.

7. Complete diagnosis is an important preliminary to satisfactory management. The value of careful auscultation in establishing the diagnosis of concomitant rheumatic heart disease is emphasized.

8. We have found no evidence to suggest that rheumatic heart disease has any influence on the development of coronary artery degeneration.

## BIBLIOGRAPHY

- BREITENECKER, L.: Ueber einen Fall von Aortitis rheumatica (Plötzlicher Tod eines 22 Jährigen Mädchens unter medikamentösem Vergiftungsvergacht), *Deutsch. Ztschr. f. d. ges. gerichtl. Med.*, 1931, xviii, 312.
- CASSIDY, M.: Coronary disease: Harveian Oration of 1946, *Lancet*, 1946, ii, 587.
- CONTRATTO, A. W., and LEVINE, S. A.: Aortic stenosis with special reference to angina pectoris and syncope, *Ann. Int. Med.*, 1937, x, 1636.
- KARSNER, H. T., and BAYLESS, F.: Coronary arteries in rheumatic fever, *Am. Heart Jr.*, 1934, ix, 557.
- KERR, W. J., LARKEY, S. V., and LARSEN, A. E.: Coronary occlusion and myocardial degeneration, *Calif. and West. Med.*, 1925, xxiii, 46.
- LEVINE, S. A., and KAUVAR, A. J.: Association of angina pectoris or coronary thrombosis with mitral stenosis, *Jr. Mt. Sinai Hosp.*, 1942, viii, 754.
- WHITE, P. D.: Heart disease, 1944, The Macmillan Co., New York, pp. 580, 611, 624.
- WHITE, P. D., and JONES, T. D.: Heart disease and disorders in New England, *Am. Heart Jr.*, 1928, iii, 302.
- ZEEK, P.: Studies in atherosclerosis: atheroma and its sequelae in rheumatic heart disease, *Am. Jr. Med. Sci.*, 1932, clxxxiv, 356.

# THE SURGICAL REHABILITATION OF THE CORONARY CRIPPLE \*

By SAMUEL ALCOTT THOMPSON, M.D., F.A.C.S., and MILTON J.  
RAISBECK, M.D., F.A.C.P., *New York, N. Y.*

REHABILITATION is being emphasized more and more in the treatment of disabled patients. The National Council on Rehabilitation has proposed the following definition of rehabilitation: "the restoration of the handicapped to the fullest physical, mental, social, vocational and economic usefulness of which they are capable."<sup>1</sup>

In general there are six groups<sup>2</sup> of the handicapped who need rehabilitation. They are: (1) the blind, (2) the deaf, (3) the neuropsychotic, (4) the tuberculous, (5) the orthopedic and, (6) the cardiacs. It is the purpose of this article to present our experience in the surgical rehabilitation of those cardiac patients who are crippled by the anginal pain of coronary artery disease.

The need for rehabilitation of these coronary cripples becomes apparent when we study their position in vital statistics. The latest figures which are available are for 1945.<sup>3</sup> In that year there was a total death rate for the United States of 1,401,719. The number one killer in this death rate is heart disease, which accounts for 424,328 or about 30 per cent of all deaths. In this group of heart disease deaths, coronary artery disease and angina account for 131,437, which is approximately 30 per cent of all heart deaths and 10 per cent of the total deaths in this year. It is estimated by the Metropolitan Life Insurance Company that in the United States in 1945 there were about four million known cases of organic heart disease. Between one-fifth and one-third or roughly from 800,000 to 1,400,000 of these have coronary artery disease. Not all of those coronary deaths were in patients who were incapacitated or crippled before death, for about 20 per cent of them die with the first attack. However, it seems fairly safe to assume that the vast majority of these patients were partially or completely incapacitated before death. It therefore becomes evident that there is a real need for rehabilitation of the "coronary cripple."

Rehabilitation for what? is the question that is frequently asked by the physician as well as the patient. We do not expect the coronary patient, crippled with angina, to become restored to a physical state beyond his former capacity. We do not expect a restoration which would allow competitive or very strenuous physical activities. We do not expect all coronary patients to be restored equally. We do have, however, a definite criterion of what does constitute rehabilitation for these patients and it consists of

\* Received for publication August 19, 1948.

From the Thoracic Surgical and the Cardiology Service of the New York Medical College, Flower and Fifth Avenue Hospitals.

the following: (1) a relief of anginal pain which may be partial or complete, (2) an increase in the exercise tolerance so that walking and ordinary travelling is possible, (3) the ability to care for the daily needs, (4) the return to some gainful occupation.

In the study and surgical rehabilitation of these patients, we have not attempted to classify angina according to its etiology. We believe that it is a result of coronary artery insufficiency which in turn produces a myocardial ischemia. The rationale of surgery in this situation is an attempt to overcome the myocardial ischemia by the production of a collateral circulation as well as the production of a myocardial hyperemia.

There have been many surgical attempts to produce a collateral circulation to the myocardium. The term "collateral" is used here in a broad sense, meaning the establishment of a new circulation in part, or a new or more efficient use of the old circulation. The theoretical weakness of these procedures is that they do not eliminate or check the continuing coronary artery disease although, in a mechanical way, they do correct the effects of the disease. Because the disease process is not eliminated, the surgical procedures cannot be considered as curative measures.

The collateral circulation can be produced in a number of ways, using a variety of technics and would appear to be the logical method in the treatment of coronary artery disease. The attachment of some vascular tissue to the heart is one of the essential features of almost all of the surgical procedures. Until recently the likelihood of producing a myocardial hyperemia as a definite part of the treatment has been overlooked.

Many tissues have been used to provide a new or collateral blood supply. Among them are skeletal muscles, omentum, intrathoracic tissue, lung or mediastinal fat, and the pericardium. Grafting tissue on the myocardium produces a collateral circulation in two ways: (1) Intra-cardiac, by the formation of new collaterals or by stimulating an increase in the size and function of these collateral channels which are already present in the heart; (2) Extra-cardiac, by the formation of new channels from the grafted tissues to the myocardium. Thus, by this method, the insufficient coronary flow is partially compensated by increasing the amount of blood supplied to the myocardium.

In our various experimental attempts to produce a collateral circulation we found, in the animals that survived the operations, two factors which were present in all the different methods. These were: (1) The surgical trauma and inflammation produced by the operation itself, which resulted in myocardial hyperemia; (2) The production of adhesions between the pericardium and myocardium. This led us to use the pericardium as the tissue from which to establish a collateral circulation.

Under normal circumstances, the pericardium is thin and appears to be almost avascular. However, the blood supply is abundant. It receives branches from the aorta, from the internal mammary, from the esophageal, from the phrenic, from the bronchial, from the mediastinal, and from the



coronary arteries themselves. These branches are ordinarily very small; nevertheless they constitute a rich source for collateral communication with the coronary arteries. Increase in the size and function of these vessels is similar to that seen in the vasa vasorum when the accompanying artery is sclerotic or stenosed.

#### EXPERIMENTAL EVIDENCE

Adhesive pericarditis may not be readily or easily produced in every instance by mechanical trauma or a host of chemical irritants. In a series of animal experiments which have been previously reported,<sup>4</sup> we attempted to find a satisfactory method for producing adhesive pericarditis and thereby grafting the pericardium on to the myocardium and finally decided upon the intrapericardial use of U.S.P. talc powder (hydrous magnesium silicate) for a number of reasons. The following results occurred constantly and therefore we considered the use of (U.S.P.) talc powder to be dependable. When introduced into the pericardial sac, talc powder produces a foreign body reaction, characterized by marked hyperemia and a fibrinous pericarditis, with little or no fluid formation. As early as 18 hours after the introduction of the powder, the pericardium becomes adherent to the epicardium at the site of the powder. After one week the two surfaces are firmly adherent, and after four weeks the pericardium and epicardium are fused as one layer of tissue. The constancy with which the powder produces an inflammatory reaction with little or no fluid formation is remarkable. This is very desirable since the presence of fluid within the pericardial sac would prevent the formation of adhesions by preventing contact between the inflamed pericardium and epicardium, and as the inflammation subsides and the fluid is absorbed, the lining membrane of the epicardium and pericardium becomes more normal so that when the tissues are again finally in apposition, adhesions do not form. Following the use of talc powder and the production of adhesions the presence of blood vessels between the pericardium and epicardium was demonstrated at subsequent operations. Also, microscopic sections of injected specimens demonstrate the presence of blood vessels between these tissues.

It has been shown by many investigators,<sup>9, 10</sup> regardless of whether the graft is muscle, omentum, or pericardium, that the postmortem injection of the vessels in the graft demonstrates that these vessels do communicate with the vessels in the myocardium. We are well aware of the controversy which exists about the value of such communicating vessels,<sup>5</sup> particularly whether an adequate amount of blood is able to pass through these vessels to the ischemic myocardium, and also whether the blood really flows toward the heart or actually away from the heart. Such scientific controversy seems to be of academic interest, particularly when the clinical result is obvious. In other words, regardless of the size of the vessels and regardless of the direction of the blood flow, the patient without the graft is unrelieved while the patient with the graft is relieved, although the scientific question may

still be unanswered. The results are easy to see, although our explanation of how these results occurred, may be at fault.

Following the introduction of the talc powder, a definite inflammatory reaction occurs, involving all of the structures in the mediastinum, the pleura, the pericardium, the epicardium and the adjacent myocardium, the esophagus and the lungs. One of the characteristic features of this inflammatory reaction is the tremendous hyperemia which is produced within a few hours. A fever accompanies this mediastinal reaction, lasting from five to 15 days and gradually subsides. We feel that this hyperemia of the myocardium not only opens up the anastomosing channels between the coronary arteries which are already present, but it also stimulates the formation of new inter-coronary channels. Because of the hyperemia, more blood is carried to and is present in the myocardium (just the opposite of myocardial ischemia). This reaction, therefore, is two fold in that it causes a dilatation of the existing vessels with a more efficient supply and distribution to the myocardium, and it also stimulates the formation of new vessels in the myocardium.

As a result of the inefficient lymphatic supply of the pericardium and the large size of the powder particle, very little, if any of the powder, is removed from the pericardial sac. The greater part of the powder remains indefinitely within the pericardial sac, fixed in the adherent tissues. In some instances, it very likely forms talcum powder granulomas and, as such, may persist for many years. Lichtman et al.<sup>6</sup> have recently reported talcum powder granulomas which were present for 10 to 15 years. One of the characteristic features of any granuloma is the hyperemia and the presence of a great number of blood vessels. Again we emphasize the fact that this is exactly the opposite of the ischemic myocardium of coronary artery disease.

By means of animal experiments we were able to demonstrate the ability of the pericardium to furnish a collateral circulation sufficient to overcome the ischemia produced by a sudden, complete ligation of a main branch of the coronary artery, when adhesive pericarditis had been previously established with talc powder.<sup>7</sup>

### DISCUSSION

Many questions have been raised as to the disadvantage or possible dangers of adhesive pericarditis. Whether by such an operation for the relief of one disease, another condition might be produced, which in time, would become as serious as the original disease? Whether the presence of an adherent pericardium might interfere with the function of the heart, or make extra work for the heart, thereby resulting in hypertrophy? We believe these questions have been thoroughly and satisfactorily answered and that adhesive pericarditis, per se, in no way interferes with the function of the heart or adds to its work.

It is necessary, at this point, to emphasize the difference between constrictive pericarditis and adhesive pericarditis. The two terms are fre-

quently confused and are often considered to be identical. However, they are entirely different. Constrictive pericarditis may or may not be adherent, and adhesive pericarditis may or may not be constrictive. The procedure which we advocate is the production of an adhesive pericarditis and this is accomplished by the technic described without producing any constriction whatever. This is proved by observations of the venous pressure at varying intervals for over nine years after the operation had been performed. One of the first signs of constrictive pericarditis is an elevation of the venous pressure. This has not occurred in any of our postoperative cases.

The question has also been raised as to whether the adherent pericardium would not become fibrous with the passage of time, and then no longer represent a sufficient source of collateral circulation, or, by reason of a fibrous nature, become scar-like and prevent the passage of blood between the pericardium and the myocardium. From our animal experiments and clinical results, we do not believe that this condition takes place, and in one of our patients who died of congestive failure, three and a half years after the operation, autopsy showed no constriction and the pericardium appeared to be a scaffold for literally innumerable macroscopic blood vessels. There was no evidence of a scar-like tendency on the part of the pericardium. Our first patient has been operated upon more than nine years ago and if such a tendency were going to occur, it seems likely that it would have become manifest within this period of time. Fluoroscopic and kymographic examinations of the postoperative cases reveal the borders of the heart to be mobile and expansile.

In coronary artery disease it is the general belief that nature is constantly producing new collateral channels within the myocardium. Given the necessary length of time or a sufficient stimulus, the rate at which these collateral channels are formed may become equal to or even greater than the rate of occlusion produced by the disease process. When such a situation exists, there is no longer an insufficiency of the coronary supply or a myocardial ischemia.

Almost every operation upon the heart is attended by a certain amount of surgical trauma and inflammation which in turn results in myocardial hyperemia. This hyperemia is the necessary stimulus to the myocardium for the production of its own collateral channels. Even though the acute hyperemia subsides and the immediate stimulus is thereby withdrawn, the increased collateral formation once started may continue for an indefinite period of time. It may well be that this stimulant, which initiates the spontaneous formation of intra-cardiac collaterals, is of greater importance than the formation of the extra-cardiac collaterals.

#### SELECTION OF PATIENTS

The selection of patients for operation depends upon the following. (1) The establishment of a positive diagnosis of coronary artery disease with

angina. This may depend upon subjective findings such as a distinct and clearly defined anginal syndrome, pain of characteristic nature and distribution with a definite relationship to effort. Or it may depend upon objective evidence of myocardial disease as revealed by the electrocardiogram, although this is occasionally absent. (2) The lack of improvement after fairly prolonged medical treatment. (3) An extreme degree of disability, corresponding to at least class 3 of The Heart Association Classification, necessitating greatly limited physical activities.

A previous coronary occlusion is not a contraindication; however, sufficient time must have elapsed to permit healing of the infarct. The two principal contraindications to operation are congestive failure and an active infarct. An attempt is made to rule out the presence of an active process by means of serial electrocardiograms, blood sedimentation rates and white blood cell counts. These three tests are performed each day for four or five days immediately preceding the operative day. If the electrocardiograms are not stable and the other two tests show an abnormal increase, the operation is postponed.

The pre- and postoperative care, and the postoperative course have been previously described in detail and will not be repeated here.<sup>8</sup>

### OPERATIVE TECHNIC

The details of the operation have been thoroughly described elsewhere and only the essential features will be mentioned here.<sup>8</sup> They consist of an incision over the fifth left costal cartilage. Approximately two inches of this cartilage are removed leaving the perichondrium. The pericardium is opened for a distance of two inches. Five to 10 minutes before the pericardium is opened the patient receives 5 c.c. of 2 per cent novocaine intravenously to desensitize the myocardium. After opening the pericardium the fluid is aspirated with a soft rubber catheter and the anterior surface of the heart is inspected and palpated for previous infarcts, adhesions and the condition of the descending branch of the left coronary artery. Approximately two drams (by volume) of dry sterile talc powder is spread over the anterior surface, the right and left and inferior borders of the heart. The powder is spread as evenly as possible so that the myocardium is white but the powder is not caked in one spot. The wound edges are protected from the powder by covering them with moist gauze. The pericardium is now loosely and incompletely closed with fine catgut and the soft tissues are closed in anatomical layers.

The novocaine is now used intravenously rather than by topical application on the myocardium. The powder (U.S.P. talc) is prepared by fractional sterilization on three different days preceding the operation and must be dry for easy application at the time of the operation. The operation can be easily performed in less than 30 minutes.

## RESULTS

The criterion for the diagnosis as well as for the decision to operate, was the ease with which angina could be produced by effort. In appraising our results, we must naturally consider the relief of pain as of prime importance, although other factors may also contribute to the rehabilitation.

Relief to a patient with angina pectoris means not only relief from the anginal pain but an increased exercise tolerance, for the two are inseparably bound together.

The exact degree of relief or improvement is difficult to measure for several reasons: (1) We have no definite objective test. The nearest approach to an objective test is the exercise tolerance test as done under basal conditions. There are a number of variables in this test so it may not be extremely accurate. (2) The degree of relief is calculated upon a subjective test, namely, relief of the patient's symptoms. The relief of the subjective symptoms is also not an accurate method, but insofar as the patient is concerned it is paramount. (3) The degree of relief may depend upon the presence of other complications such as: (a) Subsequent congestive failure which limits exercise tolerance and causes dyspnea, or; (b) Hypertension leading to hypertrophy, headaches, dyspnea and a decreased exercise tolerance. No one can predict with complete reliability the degree of rehabilitation insofar as functional activities are concerned, until the patient has actually been tested in those activities and then the degree of rehabilitation may be measured by the ability to perform such activities.

We have attempted to classify the results as follows: Poor means from zero to 33 per cent improvement. Moderate is from 33 to 66 per cent improvement. Marked is from 66 to 100 per cent improvement. The ability to care for their daily needs has been restored to all the patients who are living. With only one exception these patients have been able to return to their former occupations or to engage in other gainful occupations even though many of them had been completely incapacitated before the operation.

Several of these patients have had subsequent attacks of coronary occlusion and some of them have died as a result of the progression of the disease. However, none of the patients who survived for a period of two months after operation died a "sudden death." While this series of cases is too small to assume that "sudden death" may be eliminated by this operation, we do feel that following the operation the possibility of "sudden death" is greatly reduced. The fear of "sudden death" in these patients is sometimes very prominent, and may of itself contribute to the mortality, therefore the relief of this fear is of definite value.

Six patients died in the hospital after operation, giving a hospital mortality of 16 per cent. Three of these patients died within 48 hours of coronary occlusion. Autopsy upon two of them showed infarcts which were apparently present at the time of the operation. The other three patients died within two or three weeks after the operation—two from coronary

occlusion which developed after the operation and one from a rupture through an unhealed infarct which was discovered at the time of the operation. These cases illustrate the extreme degree to which most of our clinical material was handicapped. They also illustrate the difficulty experienced, in spite of our tests, in detecting the presence of an active or unhealed infarct just before operation. Four of the six hospital deaths were in patients who had unhealed and unrecognized infarcts at the time of operation.

TABLE I\*

	Number	Per Cent
Total number of operations	36	100
Hospital deaths	6	16
Late deaths up to seven years	5	14
Number of patients disappeared	2	6
Living at present time	23	64

\* Since the time this paper was sent for publication, 4 additional patients have been operated upon with no deaths and all with marked improvement.

As can be seen from table 1, there was a total of 36 operations. Excluding the six patients who died in the hospital and one patient who died three weeks after leaving the hospital, and the two patients who could not be followed, we have 27 patients. These patients have been observed from the time of the operation up to the present time or the time of their death. Four of these patients died from one year and five months to six years and 11 months after the operation. Twenty-three are still living and one is nine years after the operation.

TABLE II

## Clinical Results

27 patients observed from the time of operation up to nine years or the time of death

Degree of Improvement		Number	Per Cent
Poor	Zero to 33%	4	15
Moderate	33 to 66%	4	15
Marked	66 to 100%	19	70

The results shown in table 2 are based on the criteria which we mentioned earlier and are used to determine the degree of rehabilitation, although the greatest emphasis was placed on the relief of the anginal pain. Seventy per cent were markedly improved and another 15 per cent were moderately improved. According to their own estimates 85 per cent of the patients were more than 50 per cent improved. Eight patients considered themselves to be completely relieved and normal.

The four patients having poor results still have their anginal pain although there is a slight improvement in the exercise tolerance particularly after the use of nitroglycerine. Three of these patients have returned to their former or other gainful occupations. Considering the amount of pathology and the degree of incapacity we believe the results are excellent.

## CONCLUSIONS

It has been estimated that there were in the United States in 1945 from 800,000 to 1,400,000 patients suffering from coronary artery disease and angina. Many of these patients have restricted physical activities and some are completely incapacitated and are coronary cripples. It is in this last group that we have worked out a program of surgical rehabilitation.

We do not imply that all patients with coronary artery disease and angina should be operated upon. We have operated upon only those patients who were continuing to lose ground after prolonged and repeated medical treatment and who were already incapacitated because of the anginal pain.

The operation which we have described should not be considered as a cure but as a means of surgical rehabilitation for a definite group of patients. It consists in the production of a collateral circulation plus a myocardial hyperemia. The myocardial ischemia is overcome in this manner by extra-cardiac as well as intra-cardiac collaterals. The operation is simple and requires a small amount of time for its performance.

There are definite criteria as to what constitutes rehabilitation. Eighty-five per cent of the patients were moderately or more than 50 per cent improved and 70 per cent of the patients were markedly or more than 66 per cent improved.

In view of the amount of myocardial pathology and the degree of incapacity, we believe that the results of this form of surgical rehabilitation are excellent.

## BIBLIOGRAPHY

1. Report of The Baruch Committee on Physical Medicine, April 1944.
2. DEEVER, G. G.: Functional education in rehabilitation, *Surg. Clin. North Am.*, 1945, 374-381.
3. Institute of Life Insurance, New York City.
4. THOMPSON, S. A.: Development of cardiopericardial adhesions following the use of talc, *Proc. Soc. Exper. Biol. and Med.*, 1939, xl, 260.
5. BURCHELL, H. B.: Adjustment in coronary circulation after experimental coronary occlusion, *Arch. Int. Med.*, 1940, lxxv, 240.
6. LICHTMAN, A. L., McDONALD, J. R., DIXON, C. F., and MANN, F. C.: Talc granuloma, *Surg., Gynec. and Obst.*, 1946, lxxxiii, 531.
7. THOMPSON, S. A.: An operation for the relief of coronary artery disease, *Quart. Bull. Sea View Hosp.*, January 1940.
8. THOMPSON, S. A., and RAISBECK, M. J.: Cardiopericardiopexy; the surgical treatment of coronary arterial disease by the establishment of adhesive pericarditis, *Ann. Int. Med.*, 1942, xvi, 495-520.
9. BECK, C. S.: Further data on the establishment of a new blood supply to the heart by operation, *Jr. Thorac. Surg.*, 1936, v, 604.
10. O'SHAUGHNESSY, L.: Surgical treatment of cardiac ischemia, *Lancet*, 1937, i, 185.

# PHLEBITIS AND THE DIAGNOSIS OF THROMBO- ANGIITIS OBLITERANS \*

By EDWARD A. EDWARDS, M.D., *Boston, Massachusetts*

## INTRODUCTION

THE making of an early diagnosis in thromboangiitis obliterans is highly desirable. This is true not only because of the serious nature of the malady but also because its progress will usually be arrested if the patient is forced to cease smoking.

At least one-fourth of patients with the disease show an early phlebitis of their veins. This has been known since Buerger described it as "migrating phlebitis,"<sup>1</sup> yet the clinician often misses the opportunity to utilize the presence of venous involvement to make an early diagnosis. This report will try to demonstrate that by careful scrutiny of patients with thrombophlebitis, and especially with the help of the biopsy, cases of thromboangiitis may be discovered, and often before there is appreciable involvement of the arteries.

The phlebitis is of interest in late cases as well, both as an aid in establishing an otherwise presumptive diagnosis and as a sign of activity of the disease.

## CHARACTERISTICS OF THE PHLEBITIS

1. *The patient is a young person who smokes.* Thromboangiitis obliterans is overwhelmingly a disease of young males. The disease starts in the twenties or thirties. The writer has seen only one patient (Case 5) in whom it began after the age of 40. The patient is invariably a tobacco smoker.<sup>2</sup> Cases in women are extremely rare.

2. *The phlebitis may appear as an idiopathic process or may have a precipitating cause.* Often the phlebitis is initiated by trauma, and the true diagnosis is suspected only through migration of the lesion or its excessively long duration.

3. *The superficial veins are always affected; the deep veins possibly so.* The saphenous vein is most commonly attacked. Involvement of a vessel on the dorsum of the foot, or in the toes, is quite characteristic of the process, since one does not see phlebitis of other causes originating here. Any portion of the superficial veins of either extremity may be implicated. Occasionally, the phlebitis is noted in the external jugular or its tributaries.

It is uncertain how often the deep veins are inflamed in the early stages of the disease to form a part of the migrating phlebitis. That deep phlebitis of small veins is a frequent part of the process is suggested by the oft-occur-

\* Received for publication March 12, 1949.

From the Department of Surgery, Tufts College Medical School.

Aided by a grant from the Charlton Research Fund, Tufts College Medical School.



ring deep tenderness, cyanosis, or vasospasm without loss of the pulses. Tender cyanotic toes are frequently seen, and suggest activity in the digital vessels—perhaps of both veins and arteries. Thrombophlebitis of the large, deep veins, such as the femoral, is rare in this type of migrating phlebitis.

4. *The major arteries are ordinarily involved not at all, or only to a minimal degree at the time of a first bout of the phlebitis.*

5. *The phlebitis extends and migrates.* The process typically extends along the superficial veins from its initial focus, both by continuity and by distant involvement of new areas. This accounts for the expression "migrating." The phlebitis does not necessarily skip from one limb to another. It may remain in the initially involved extremity throughout its long duration.

The appearance of the disease in small areas may give rise to the impression that the disease is a dermatologic one.

6. *The process is long lasting and tends to spontaneous reactivation.* A single bout may last weeks, months, or years. At the end of that time, there may still be continued or recurrent inflammation in the original focus, as well as in others. In some patients, recurrent bouts are observed, but they rarely are more than two or three in number.

7. *Pulmonary embolism is rare, except from femoral vein thrombosis.* The author knows of one fatal, and one non-fatal instance, each from an obvious process in the femoral vein. Kahn<sup>3</sup> reports an instance of pulmonary embolism from a phlebitis of the deep veins, and attests to the rarity of this complication.

8. *Biopsy of the vein may reveal a characteristic lesion.* The vessels in thromboangiitis obliterans present three types of pathology: inflammation, thrombosis and intimal proliferation.<sup>4</sup> These processes may occur singly or together. It is only the inflammation which may be said to be characteristic in this disease, though there is no picture which is rigidly pathognomonic.

The inflammation involves all the coats of the vessel, and extends into the perivascular tissue. Lymphocytes, histiocytes, and fibroblasts are prominent; polymorphonuclear leukocytes vary in their number. The elastic laminae are not destroyed, but may be thickened or split ("reduplication"). These findings may be said to be consistent with the diagnosis of thromboangiitis obliterans.

More typical and diagnostic is the presence of an intraluminal granuloma, occurring with or without a thrombus, and made up of the above-named elements plus foreign-body giant cells (figure 1). Though the cells are similar to those of the tubercle, the architecture of the granuloma is not as well ordered as in tuberculosis. Aggregates of cells, similar to those of the granuloma of thromboangiitis obliterans, occur in vessels in other diseases, but are not found within the lumen. Thus, giant cells may be seen about calcific plaques in the walls of sclerotic arteries, and in the *media* of the artery in temporal arteritis.

The typical granuloma of thromboangiitis obliterans is found rarely in involved arteries, uncommonly in the deep veins, but with great frequency

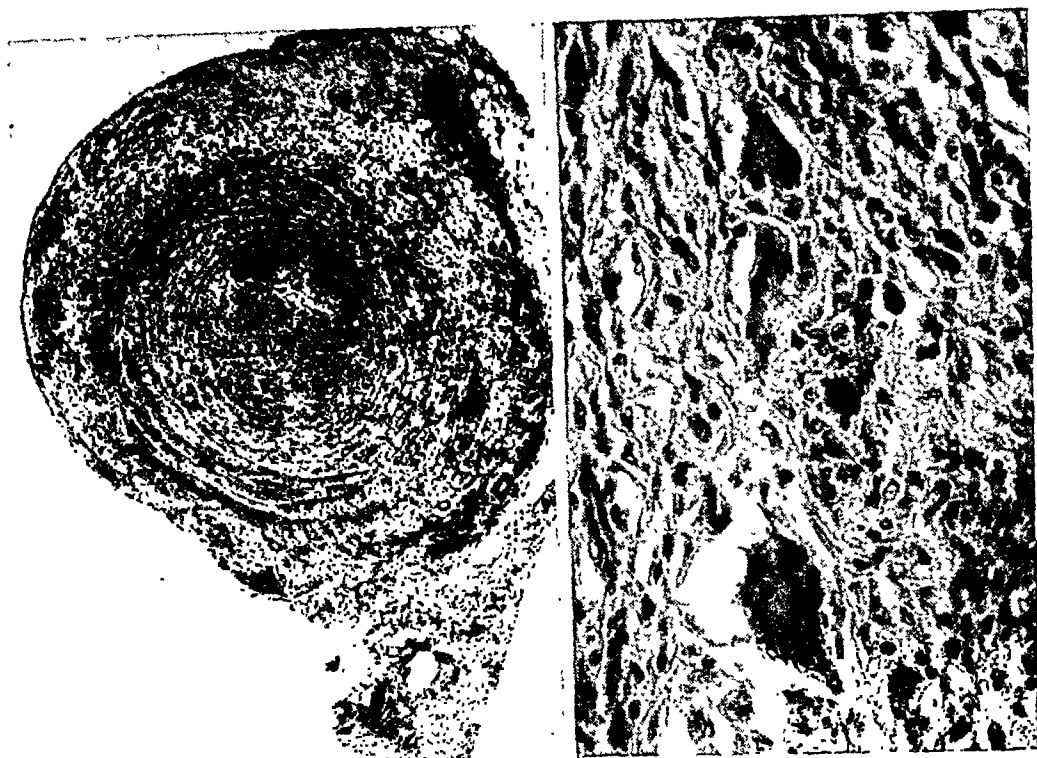


FIG. 1. The characteristic lesion of thromboangiitis obliterans.

*Left*, section of a saphenous vein involved in a migrating phlebitis. There is marked inflammation, with cellular infiltration throughout the entire vessel, extending to the perivascular tissues. Giant cells are present in the intraluminal granuloma. (Reprinted by permission from New Eng. Jr. Med., 1939, ccxxi, 251.)

*Right*, detail of the granuloma. (Reprinted by permission from Arch. Path., 1943, xxxv, 241.)

in the superficial veins during the migrating phlebitis. It should be sought for in vessels showing clinical signs of inflammation, and may be found in segments which have been inflamed for months or years.

Biopsy of an inflamed vein is therefore a diagnostic procedure of great value, and involves no special hazard. If the granuloma is found, and if the clinical picture is suggestive, the diagnosis is sure, even when an arterial lesion cannot be found. In the absence of the granuloma, a widespread inflammation of the vein extending to the perivenous tissue is suggestive of the diagnosis, but the author cannot say how much weight should be given to this finding.

#### MANAGEMENT

Data for the diagnosis of a case of phlebitis of uncertain origin will be obtained from a thorough history and physical examination. The laboratory will aid in uncovering blood dyscrasias. The clinical picture, occasionally aided by a biopsy, will establish the diagnosis of thromboangiitis obliterans. It is worth emphasizing that in the middle-aged patient a migrating phlebitis clinically resembling that of thromboangiitis obliterans has been found in association with visceral carcinoma, especially of the tail or body of the pancreas.<sup>5</sup> In these circumstances, the thrombophlebitis is even more

migratory. Indeed, it is widespread and recurs not once or twice, but many times in quick succession.

Once a diagnosis of thromboangiitis obliterans is established, the patient must immediately stop all use of tobacco. In the absence of ischemia, this may be all that is necessary, and the phlebitis will subside in days or weeks. If the pain and edema of the phlebitis are severe, and especially if there is much vasospasm, sympathectomy has been found to give quite immediate relief. Anti-coagulants or deep vein ligation may be added to the treatment if there is evidence of thrombophlebitis of the popliteal or femoral veins.

## ILLUSTRATIVE CASE REPORTS

### *A. Value of the Biopsy in Early Diagnosis*

*Case 1.* A 26-year-old machinist bruised his right leg at work, setting up a thrombophlebitis of the superficial veins. A segment of inflamed saphenous vein was excised, but the inflammation continued in neighboring veins. When he was seen 11 months after the injury, the phlebitis was still present. Pulsations were present in all the major arteries.

A review of the pathologic slides showed the typical intraluminal granuloma. The phlebitis subsided in a few days after a right lumbar sympathectomy and the cessation of smoking. Three years later, he had mild claudication in the left calf, and had lost the pulsation in the posterior tibial artery. Pulsation returned after a left lumbar sympathectomy. He is now symptom free, eight years after the onset of phlebitis.

*Case 2.* A 26-year-old mail carrier had suffered a thrombophlebitis of the right saphenous vein after a contusion. When seen two years later, there was continued, active thrombophlebitis of every sizable superficial vein of the right lower limb, from the groin to the ankle. The pulses of the lower extremities were unequal, and there was objective evidence of mild ischemia of the feet.

Biopsy of a superficial vein in the right leg showed the typical picture of thromboangiitis obliterans, including the granuloma. It was learned later that the patient's father had died of Buerger's disease at 38. Bilateral lumbar sympathectomy was performed, and the patient stopped smoking. The phlebitis subsided at once.

*Case 3.* A 28-year-old shoe salesman presented a thrombophlebitis of the superficial veins of the left lower limb, which had started spontaneously on the foot, and had progressed to the thigh in six weeks. All major arteries showed pulsations of good quality. Biopsy of the saphenous vein showed the widespread inflammation and intraluminal granuloma of thromboangiitis obliterans. The phlebitis subsided two weeks after the patient stopped smoking.

### *B. Significance of the Phlebitis in Late Cases*

*Case 4.* (Reported through the courtesy of Dr. M. K. Bartlett.) A draftsman of 49 suffered from a phlebitis which started spontaneously on the right foot and ascended to the calf. At the age of 32, he had had a phlebitis of the right calf, initiated by a contusion, and lasting six weeks. At 38, he had a second attack in the left leg and thigh, after a bruise of his ankle, and lasting five months. At the time of his latest and third attack of phlebitis, no pulses were discernible in the left foot. A biopsy of the inflamed vein on the right foot showed the granuloma of thromboangiitis obliterans and finally established the nature of the disease.

*Case 5.* A shipping clerk began to have claudication at the age of 43. When

first seen, at 49, there were no pulsations below either popliteal level. The onset of symptoms after the age of 40, the absence of a history of phlebitis, and the slow course of his illness led to a probable diagnosis of arteriosclerosis.

At the age of 51, a phlebitis started at the right ankle and dorsum of the foot after a sunburn, and slowly ascended in the leg. Biopsy of the inflamed vein showed the typical granuloma and extensive inflammation of thromboangiitis obliterans, and established the true diagnosis.

*Case 6.* A 28-year-old laborer had suffered from gangrene of a toe after a crushing injury. The ulceration, amputation, and final healing occupied two years. After this, he was symptom-free for a year. He had not stopped smoking. One month prior to being seen, the right foot became painful and swollen. There was evidence of thrombosis of the popliteal artery, and simultaneously, a thrombosis of the veins of the dorsum of the foot, and of the leg. Biopsy of a vein showed the granuloma and other changes of thromboangiitis obliterans. The limb came to amputation.

In this patient, the appearance of thrombophlebitis coincided with activity of the disease in the arteries.

### CONCLUSIONS

The presence of a migrating phlebitis of uncertain origin, or of unusual course, may allow a diagnosis of thromboangiitis obliterans to be made before the arteries are involved. Both the clinical characteristics of the phlebitis and its appearance by biopsy are important in establishing the diagnosis.

In later cases, the phlebitis may aid in differentiating the arterial lesion from arteriosclerosis. The phlebitis may also serve as an index of activity of the disease in the arteries, or as a sign that the patient is continuing to smoke.

### BIBLIOGRAPHY

1. BUERGER, L.: The circulatory disturbances of the extremities, 1924, Saunders, Philadelphia.
2. SILBERT, S.: Etiology of thromboangiitis obliterans, Jr. Am. Med. Assoc., 1945, cxxix, 5-9.
3. KAHN, J. W.: Thrombophlebitis of the deep veins in thromboangiitis obliterans, Surg., Gynec. and Obst., 1946, lxxxiii, 449-452.
4. EDWARDS, J. E., and EDWARDS, E. A.: The venous valves in thromboangiitis obliterans, Arch. Path., 1943, xxxv, 242-252.
5. EDWARDS, E. A.: Migrating thrombophlebitis associated with carcinoma, New Eng. Jr. Med., 1949, ccxi, 1031-1035.

# RED BLOOD CELL SENSITIVITY IN CAUCASIANS \*

By PAUL M. NEUDA, M.D., *New York, N. Y.*

IN a previous paper <sup>1</sup> I had reported that the sickle-inducing substance, the blood-group-enzyme (BGE), which was originally found in feces, was also present in the blood in certain diseases including sickle cell anemia. While, however, the BGE in feces is a normal constituent, the presence of this substance in the blood in disease is apparently an abnormal finding. In the presence of red cell sensitivity, for example, the BGE in blood might be a red cell damaging agent. This could possibly apply as an explanation to sickle cell anemia.

The BGE was, however, not only found in the blood of Negroes but also in the blood of Caucasians. Since "red cell sensitivity to the BGE" presumes the interaction of two factors, the BGE on the one hand, and a preëxisting red cell quality called "sensitivity," on the other, the question arose if there might be present in the Caucasian a pathological red cell figure comparable to the sickle cell of the Negro, and what this figure might be. This question is dealt with in the following study.

The method used in this investigation was that described in my previous papers.<sup>1, 2</sup> Red blood cells, washed three times, were taken up in normal saline to an approximately 5 per cent suspension. As a rule, the blood cells were washed immediately after withdrawal. Traces of these cells were transferred by means of a glass rod into a drop of a BGE-broth produced either from fecal material or from certain bloods. The changes in the red cells appeared after a time interval which varied from a few minutes to several hours. The wide variation in time depended apparently on differences in both the red cell sensitivity and the strength of the BGE. In the sickling blood of the Negro, where red cell sensitivity is extremely high, the cell changes appeared in a few minutes after exposure to the BGE. In other bloods where red cell sensitivity was found low, as in Caucasians, characteristic changes appeared after five to six hours.

Although hundreds of cases have been investigated by this method in the past six years, this study is confined to the material seen between August 1946 and September 1947. During this period, 126 cases were studied of which 76 were Caucasians, 47 were Negroes, 2 were Malaysians and 1 a Puerto Rican.

Before describing the results of this investigation it is necessary to describe in short the typical chain of events which occurs when red cells of a Negro suffering from sickle cell disease are exposed to the action of the BGE.

The development from a normal round cell to the "sickle" does not take

\* Received for publication October 21, 1948.

From the Achelis Laboratory, Lenox Hill Hospital, New York.

place in a simple fashion. There are four separate well-defined stages which characterize its development under BGE influence. Each of these stages which occur in succession, represents a complete step in the gradual formation of the "sickle."

It must be emphasized, however, that the BGE does not create any new figures. There is no essential difference in the appearance of the sickle cells produced by the BGE and those produced by anoxia in the sealed wet preparation. However, either because of the specificity of the BGE or its power, the successive changes in the red cells occur with a clarity in the details that are never observed in the simple sealed wet preparation.

The first stage is an enlargement and simultaneous thinning by stretching, of the disc. This picture is in some cases due to the uniformity, of extraordinary beauty.

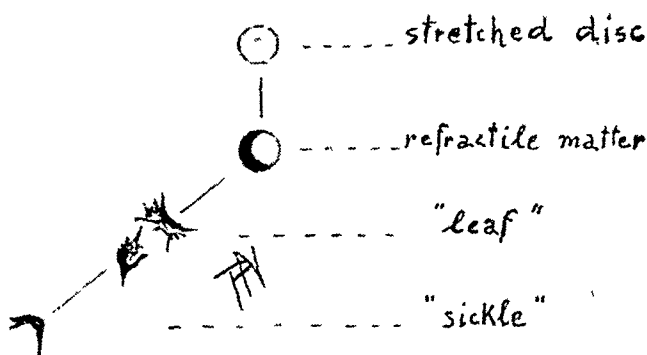


FIG. 1. The four regular stages in the sickle cell development under BGE influence.

The second stage is a striking change in the distribution and appearance of the hemoglobin. There are formed a highly refractile dense area or areas, while the remainder of the cell gets a smooth and paling appearance. Due to the rapidity of the change, stages one and two are often found together.

The third stage is a figure which for convenience because of its characteristic silhouette, may be called "leaf."

The fourth stage is the "sickle" which develops from the "leaf" after it has lost most of its prongs.

These four steps in the sickle cell development\* under BGE influence, more precisely in a feces-enzyme-broth, are shown schematically in figure 1.

Although the phenomenon has received its name from the "sickle"-shaped end stage, for reasons which will become later fully clear, the third stage or the "leaf" must be regarded the most significant of all. For the present, it is sufficient to state that the "leaf" is the first sign of actual cell destruction. While stages one and two are reversible, stage three the "leaf," is irreversible. It is of great clinical interest that the sickling process may in some cases exhaust itself with the third stage so that no further development to the

\* To be described and discussed more in detail in a subsequent paper.

"sickle" takes place and the "leaf" remains the only sign of the underlying sickling condition.

Of an obvious great significance is the fact that stages one and two are not restricted to Negroes, but can also be seen in Caucasians. Consequently, they are not characteristic of Negro blood as are the "leaf" and the "sickle." There is, however, a red cell figure in the Caucasian, which is as significant of red cell destruction as is the "sickle" of the Negro. It was first observed as an intermediary figure of the sickling phenomenon in the Negro. Though under ordinary conditions, it is only occasionally encountered, it is regularly produced under certain experimental conditions. As described below, when in the mixture of erythrocytes and BGE, plasma plays a major rôle, the development of the "leaf" and the "sickle" is preceded by the appearance of a new figure. This consists of a clear cell fragmentation with the formation of several pieces in "block"-form. This phenomenon may conveniently be called "block"-partition. There is but one interesting difference in this figure as it occurs in the Negro and the Caucasian. In the Negro with sickle cell disease, the several "blocks" resulting from cell partition continue their development to the "leaf" and the "sickle," while in the Caucasian this figure "block"-partition is final. These respective developments are schematically shown in figure 2.

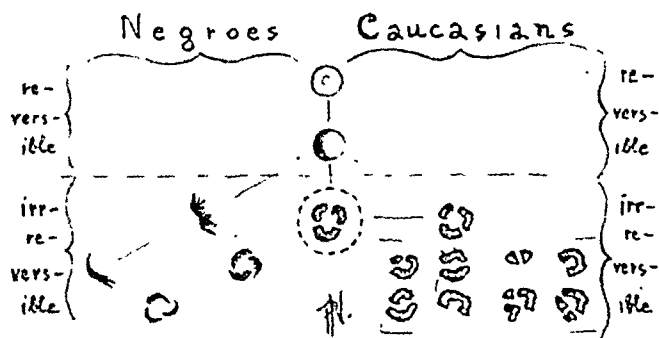


FIG. 2. The red cell sensitivity figures under BGE influence, as they occur in the sickle cell diseased Negro and the Caucasian.

As sickle cell disease does not occur in Caucasians, "block"-partition must be considered as characteristic of an idiopathic condition. This assumption is supported by the fact that "block"-partition as an idiopathic condition, exists also in Negroes not afflicted with sickle cell disease. The partition figure may consist of two, three or more "blocks." In this idiopathic condition, in both Negroes and Caucasians, where separated "blocks" are the remainders of cell destruction, some very characteristic figures are usually seen. They are the figures shown in figure 2 in brackets.

The intermediary "block"-partition figure in sickle cell disease (encircled in figure 2), which may or may not be met in the usual routine investigation, is regularly met, if plasma is added to the reaction between washed red cells

and the BGE. Mere traces of plasma are capable of accomplishing this, as is shown in the following experiment.

Two BGE media, distinct with regard to the plasma content, one a usual feces-enzyme-broth (Schiff), the other a plasma-enzyme-broth (Neuda), were compared with regard to their respective action on the washed cells of a negress (P. G.) suffering from sickle cell disease. Result: the cells suspended in the feces-enzyme-broth, were at the end of 28 minutes transformed directly into "leaves" and "sickles," there was no sign of partition of the cells; the cells suspended in the plasma-enzyme-broth, however, revealed after 34 minutes widespread "block" partition with numerous "leaves" and "sickles" developing from the disconnected parts. Figures 3a, a photomicrograph, and 3b, a drawing, show block-partition and sickle formation together as obtained in this experiment.



FIG. 3a.

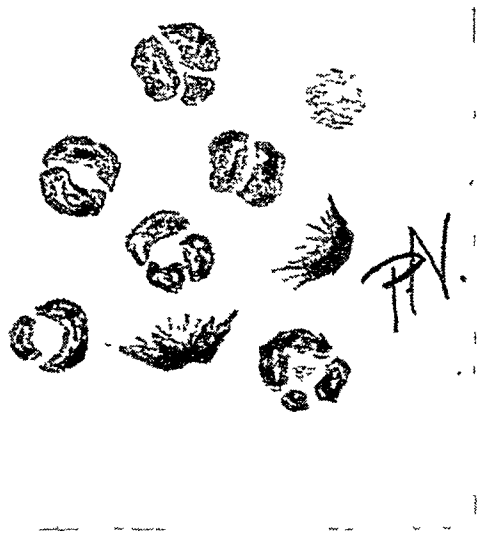


FIG. 3b.

Block-partition and sickle formation together, at left in a photomicrograph, at right in a drawing of selected figures (case F. G.).

This combined BGE-plasma-influence was demonstrated in repeated tests with a plasma-enzyme-broth. It was also reproduced with a feces-enzyme-broth if traces of plasma were added. The influence of the plasma seems to be of a general character and will require further investigation for its elucidation. In these experiments, always plasma of the same blood group was used.

The common occurrence of block-partition as an intermediary figure in sickle cell disease and as an idiopathic figure in both Caucasians and Negroes, in the latter in the absence of sickle cell disease, indicates that this figure very probably belongs to the same type of blood destruction as the "sickle." This is what I had previously termed "hemolysis of sickle cell type."

This concept is supported by the analysis of the 126 cases in this study. Block-partition was found in a significantly higher percentage in the blood



of Negroes than of Caucasians. Of 14 cases, in which block-partition was observed, 11 were Negroes and 3 were Caucasians. Comparing the number of white patients (76) with colored (47), the greater frequency of this form of blood damage in the colored race is obvious: 23.4 per cent of the Negroes and 3.9 per cent of the Caucasians.



FIG. 4. Selected figures of block-partition in a negress. Washed red cells in a feces-enzyme-broth. Appearance after six hours.

The following two figures show block-partition in a Negro and a Caucasian, respectively. Figure 4 shows the red cell figures in a negress (C. Gu.) with pelvic inflammatory disease and an unexplained anemia, but without sickle cell disease.

Figure 5 shows the red cell figures in a Caucasian (H. K.) with a polyglandular endocrine disturbance. The similarity of these figures with the figures obtained from the blood of the negress, is striking. The "claw"-like forms deserve special mention since they are so characteristic of this type

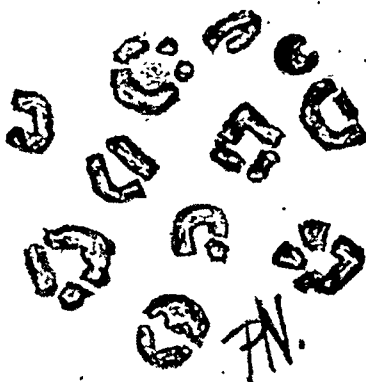


FIG. 5. Selected figures of block-partition in a Caucasian. Washed red cells in a feces-enzyme-broth. Appearance after five hours.

of blood destruction. They originate apparently by the loss of one "block" in the original circumference of the destroyed cell.

The traceable higher frequency in incidence of block-partition in the colored populace can be explained, at least partly, by the proved intimate connection which exists between this condition and the sickle cell disease. Of the above mentioned 11 Negroes exhibiting block-partition, six were afflicted with sickle cell disease. One might conclude that "hemolysis of sickle cell type" is more widespread in Negroes than in Caucasians. This may actually be so. However, the incidence of this type of hemolysis in Caucasians is not as rare as the above figures would indicate, since there are still other forms of this type of cell damage which can be met as often in Caucasians as in Negroes. A report on these other forms of "hemolysis of sickle cell type" will appear elsewhere.

Of a special interest will be the question, in which diseases can block-partition be expected? On the grounds of the evidence at our disposal, the following can be said. Block-partition tendency of red cells, as revealed by the use of the BGE, is a sign of an inherent liability, called sensitivity. It has, apparently, the same significance as the sickling tendency, though, as a disease, it is of a minor order. As in sickle cell disease, it is frequently found combined with anemia. Unlike sickle cell disease, however, it is not restricted to Negroes but occurs also in Caucasians. In the Negro, the phenomenon is clearly observable only in the absence of the sickling condition, since in its presence, the several blocks rapidly undergo further change to sickles.

The following are the clinical diagnoses in the cases in which block-partition has so far been found: liver disease, especially cirrhosis of the liver, Hodgkin's disease, a malignant ovarian cyst, endocrine disturbances, anemias of undetermined origin and sickle cell disease. Most of the information hitherto obtained on this curious condition, we owe to the sickle cell disease. This makes sickle cell disease a most important object of study for the further elucidation of the mechanism acting in "hemolysis of sickle cell type."

#### BIBLIOGRAPHY

1. NEUDA, P. M.: Red blood cell sensitivity to the blood-group-enzyme, *Science*, 1947 cvi, 296-297.
2. NEUDA, P. M., and ROSEN, M. S.: Preliminary report on a rapid method for diagnosing sickle cell disease, *Jr. Lab. and Clin. Med.*, 1945, xxx, 456-458.

# ELECTROKYMOGRAPHY OF THE HEART AND GREAT VESSELS: PRINCIPLES AND APPLICATION \*

By BERT R. BOONE, M.D., GEORGE F. ELLINGER, M.D., F.A.C.P., and  
FREDERICK G. GILICK, M.D.

## INTRODUCTION

THE electrokymograph is an instrument which permits the graphic registration of the movements of the heart and great vessels. Many investigators of the cardiodynamics of health and disease have pointed out the importance of studying these movements. Beginning with observations made by the physiologists on the exposed heart, an increasing fund of knowledge has been accumulated. Fluoroscopy, roentgencinematography,<sup>1</sup> and roentgenkymography<sup>2, 3, 4</sup> have all contributed basic information. Each method has definite limitations and only fluoroscopy has wide clinical usage. There is need for methods which can be more easily applied to physiological and clinical usage in intact subjects.

During the past few years several attempts have been made to develop improved graphic methods utilizing the roentgenoscope. These are based on the fact that variations occur in the transmission of x-rays through the heart and/or past its borders as the heart undergoes its phasic volumetric and positional changes. In Heckman's<sup>5</sup> apparatus, these variations in amount of transmitted x-ray are transformed to light variations on the regular fluoroscopic screen. The variations in intensity of light are then picked up by a photo-electric cell which converts them to current changes. Marchal<sup>6</sup> and Hjelmar<sup>7</sup> developed somewhat similar devices. Hjelmar later used a Geiger-Mueller counter, placed directly over the heart, as the sensing device to record x-ray changes. Each of these pick-up and conversion devices was so adapted that variations in current produced in it could be recorded by a galvanometer. Between 1944 and 1947, Henny and Boone, working with the same principle, adapted a modern type photo tube to develop an instrument which they named the electrokymograph.<sup>8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18</sup> Used with the roentgenoscope and electrocardiograph, it produces a permanent tracing—the electrokymogram (EKY), which faithfully reflects the movements and density changes of a chosen portion of the border or body of the heart or great vessels.

This paper summarizes observations made to date, on the electrokymograms of a large group of normal individuals, and indicates some of the significant variations noted in patients with cardiovascular disease. Continued investigations must be made before all the details of the normal va-

\* Received for publication March 20, 1948.

From The National Heart Institute, U. S. Public Health Service, Bethesda, Md.

riations can be defined and before it becomes possible to lay down the boundaries between normal and pathological.

### THE INSTRUMENT AND TECHNIC

The electrokymograph<sup>8,9</sup> was specifically designed as an attachment for use with the roentgenoscope and electrocardiograph. When these three units are utilized together, for the purposes of electrokymography, the basic function of each is as follows; the roentgenoscope provides the means for observing the cardiovascular silhouette of a subject and for positioning the electrokymographic pick-up unit over a selected area; the electrokymograph converts the motions and density changes of such selected points to corresponding current variations; and the electrocardiographic galvanometer records these variations on moving bromide paper (an electrokymogram). A carotid sphygmogram is simultaneously recorded for timing and orientation purposes.

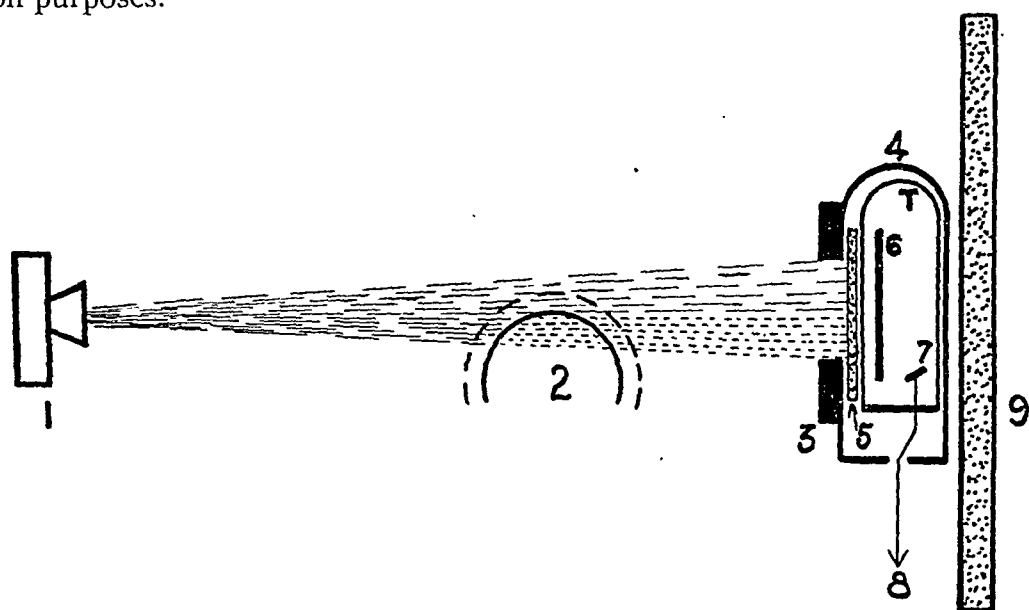


FIG. 1. Schematic illustration demonstrating principles of electrokymograph.

1. Source of roentgen-ray.
2. Heart in systole and diastole.
3. Limiting lead aperture.
4. Copper housing.
5. Small fluorescent screen.
6. Light sensitive surface of photo-multiplier tube (T).
7. Current collecting anode.
8. Connection to galvanometer.
9. Large fluoroscopic screen for general observation.

The electrokymograph consists principally of a roentgen-ray sensitive pick-up unit and its power supply. As shown in figure 1, the pick-up unit is made up of a lead diaphragm (3) with an aperture 5 by 20 mm., which serves to frame or limit the area to be recorded. Behind the diaphragm is placed a piece of fluorescent screen (5) with its light emitting surface close

to and facing the photo-sensitive surface (6) of an RCA 931-A multiplier phototube (T). The pick-up unit is conveniently mounted on the patient side of the ordinary fluoroscopic screen (9) so that both it and the subject's cardiovascular silhouette can be viewed simultaneously. Then as the heart changes in systole and diastole, varying amounts of x-ray activate the small fluorescent screen, producing variations in light. The phototube responds to these light variations and produces corresponding current variations. These current variations are directed into an electrocardiograph\* and recorded on moving bromide paper. A rotating mechanism, operated from the fluoroscopist's side of the large screen, provides means of aligning the long axis of the photo-tube aperture parallel to the direction of motion of the cardiac border being examined.

The evaluation and interpretation of the EKY are greatly facilitated by the simultaneous recording of some well-known cardiodynamic event. We find the carotid sphygmogram most satisfactory for routine purposes, though we use the electrocardiogram or stethogram at times. The carotid curve has the advantage of relative simplicity of recording and interpretation and gives a mechanical event to compare with the "mechanical" electrokymogram. Our carotid-pulse recorder<sup>9</sup> utilizes an air conduction system. It consists of a pick-up cup on an adjustable neck clamp, a rubber tube from the cup to the recording mechanism and a recording tambour with a pointer centered in the optical beam of the ECG.

Luisada and Fleischner<sup>19, 20</sup> subsequently reported on the use of the electrokymograph and stethograph and suggested the term fluorocardiography for this method. The term electrokymography has been widely used and has been adopted by two commercial companies† producing instruments for recording cardiac, vessel and other border motions which utilize the principles herein described. Therefore, it would appear confusing to introduce a new term for each combination of an electrokymogram and carotid sphygmogram, electrokymogram and electrocardiogram, or electrokymogram and stethogram. Also, the instrument has been adapted for use other than the study of the heart, for instance, to record the motions of mediastinal masses, as a photo-electric plethysmograph, and more recently as a recorder in ballistocardiography.

Specific instructions may vary for using the Cambridge or the Sanborn electrokymograph. In general the procedure of operation is as follows: the recording galvanometer is turned on and standardized as for electrocardiography. The power supply which energizes the photo-multiplier tube is turned on. The fluoroscope is set at 85 kv. and between 2.5 and 3 ma., and the patient is then placed in position for examination. The carotid-pulse clamp is adjusted to the patient's neck so that an adequate amplitude of carotid-pulse shadow excursion is obtained. The part or parts to be ex-

\* While both types of electrocardiographs have been utilized, most of our work has been done with the string galvanometer.

† Cambridge Instrument Company, Inc. and Sanborn Company.

amed are viewed through the fluoroscopic screen and the photo-tube mounting is swung into position, automatically centering the tube in the central beam of the x-ray. By manipulation of the fluoroscopic screen and rotation of the tube, the aperture of the pick-up unit is aligned so its long axis lies parallel to the direction of motion of the part to be studied (figure 2).

As soon as satisfactory alignment is accomplished, the technician introduces the signal into the galvanometer of the ECG by turning the "volume control" of the electrokymograph up slowly. The amplitude of the galvanometer excursions is controlled by this "volume control." The carotid-pulse shadow is again checked. When amplitude and alignment are satisfactory the patient is requested to "stop breathing" in the mid-phase of normal respiration and the ECG camera is started.

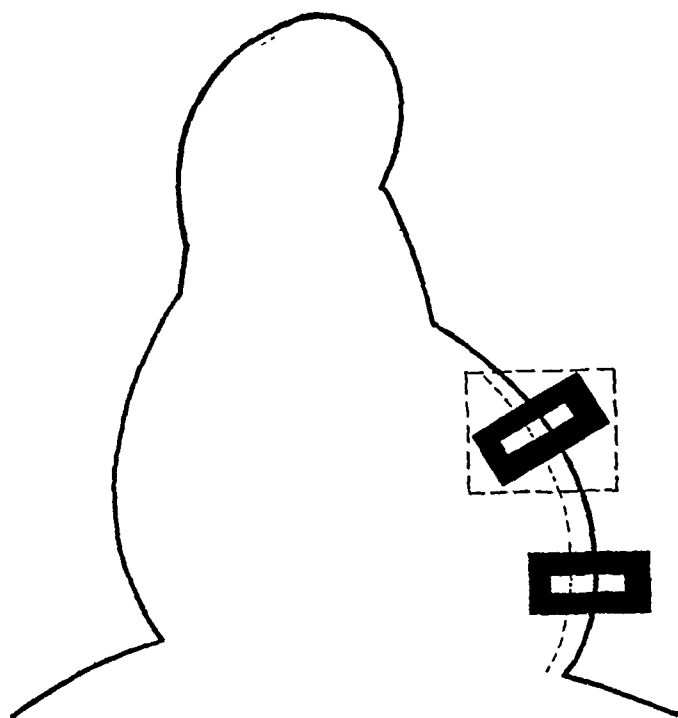


FIG. 2. Illustrating application of aperture of pick-up device over two points on cardiac silhouette. Note long axis parallel to direction of motion of borders, i.e. perpendicular to border. Moving shadow remains within aperture. After proper alignment of pick-up device, roentgen beam is coned by roentgenoscopic shutters (dashed square).

While no standard patient positions or views have been established for "routine" electrokymographic examination of the heart, the following segments of the cardiovascular silhouette have been examined in most instances: (1) Posterior-anterior projection; left ventricle (lower, middle, and upper), pulmonary artery, aortic knob, right atrium. (2) Right-anterior-oblique projection; left ventricle (lower and middle), pulmonary artery (when not obtained in posterior-anterior projection) and dorsally the areas of the right and left atria. (3) Left anterior-oblique projection; left ventricle (lower and middle), left atrium, ascending aorta, right ventricle.

The posterior-anterior projections are routinely used. When using the oblique projections, the subject is rotated to whatever degree necessary to bring a desired chamber or vessel into silhouette. As is well known, there is wide individual variation in the cardiovascular silhouette of normal subjects and in the presence of cardiovascular disease. Therefore, the patient position and the precise degree of rotation needed to examine a particular chamber or vessel will vary.

The time required to complete an EKY will depend upon the speed and teamwork of the fluoroscopist and technician and on the number and length of records taken. Our average examination includes about 12 records and requires less than 10 minutes. Exposure to radiation during such a "routine" EKY amounts to less than five minutes. This amount of radiation under our conditions of operation is well within the margins of safety.

### NORMAL ELECTROKYMOTRAPHY

This report is based primarily on the study of electrokymographs of 140 medical students and nurses, age 17 to 32, who had no clinical evidence of cardiovascular disease. The entire group had two electrokymographic examinations done two to three months apart and in some instances a third examination. In addition, a smaller number of normal persons of intermediate age, a large group of older men and selected subjects with cardiovascular disease have been examined. Altogether approximately 500 subject examinations have been made in the past two years.

Certain physical characteristics, common to all electrokymographs, should be pointed out before discussing the records from specific chambers or vessels. All can be studied as to their configuration, amplitude and timing. A study of configuration shows that electrokymographs are made up of ascending and descending limbs, peaks, plateaus and other complexes. The electrokymograph is so connected to the galvanometer that a descending limb results from the medial movement of a particular border, a decrease in density of a part, or any combination of these changes which allows increased transmission of x-rays. An ascending limb results from lateral movement of a border, an increase in density, or any combination of these changes which decreases the transmission of x-rays. A rapid change in density or border movement produces a steeply sloped limb, while slow changes produce more gradual slopes. When a part is not moving or changing density, or when complex movement and density changes exactly counteract one another, a straight line is recorded. Peaks, domes, notches, etc. result from changes and shifts in balance of border movement and density, which occur as the heart undergoes volumetric, positional or shape changes during its cycle of activity.

A method of standardizing amplitude has yet to be perfected. At present the operator determines the amplitude of the curve by altering the volume control setting. Arbitrarily the amplitude is set so that it is approximately

equal to the cycle length in millimeters which gives a record with good characteristics for reading. The amount of motion at two points can be compared by taking records with the identical setting of the volume control. This gives an approximation of the relative amount of motion but the curves do not represent quantitatively the amount of movement. When recording from one point of the silhouette, variations in amplitude at a constant volume setting are significant. Another point to be remembered is that the instrument registers only that component of border movement which occurs at an angle to the axis of the central x-ray beam. When the movement is at a right angle, the greatest amplitude will be recorded. Movements in the same axis as the beam register only when they are accompanied by density changes of the part. These density and movement changes may then merge with or neutralize one another and thus alter the amplitude of the EKY.

The timing of the curves can be accurately determined. Time lines on the record are the same as for electrocardiography, i.e. each small space  $\approx 0.04$  sec. We believe the records can be read with an accuracy of  $\pm 0.01$  sec.

Many observations presented here substantiate and some differ from those made previously with the roentgenkymograph and other instruments. No attempt will be made to give individual credit to the many workers who contributed the remarkable fund of basic data on which we have drawn freely.

*The Ventricular EKY.* The left and right ventricular electrokymograms have basically similar configurations, though they may differ in detail. Each cycle consists of a major descending limb due essentially to the medial movement of the ventricular border during systole, and an ascending limb associated with lateral movement of the wall in diastole. Superimposed upon these two basic limbs are peaks, plateaus, and other variants. The records are surprisingly similar to volumetric curves of the ventricle obtained by direct cardiometer methods in animal experimentation.<sup>21</sup> Though they reflect volumetric changes to a remarkable degree, they also show effects from pendulum movement, rotation and shape changes of the heart.

The interpretation of the EKY from the carotid sphygmogram has been previously described.<sup>10</sup> The onset of the major ascending limb and the cleft of the incisura on the carotid curve are identified. Projection from these points to the EKY helps to identify the onset of ventricular ejection and the onset of isometric relaxation respectively. In many records the onset of the descending limb of the incisura is well defined and identifies the beginning of protodiastole; in some, ventricular isometric contraction is registered on the pulse wave. Starting from these points, the application of known facts concerning the phases of the cardiac cycle permits completion of the analysis.

When studying a right ventricular record, it is best compared with another right heart event, the pulmonary artery EKY. Since these are not simultaneously recorded, the carotid sphygmogram is used as a common time reference curve. A convenient method is to make a tracing on trans-



parent paper\* of the EKY of the pulmonary artery. A vertical line is drawn on this tracing through the ejection point of the accompanying carotid curve. This transparency is then superimposed over a right ventricular record so that the vertical mark is aligned with the ejection point of the carotid sphygmogram which accompanies the ventricular EKY. When cycles of equal length are chosen, this method greatly facilitates the comparison of the activities of various chambers and the study of the effect of the activities of one chamber upon another. Simultaneous recordings of the stethograph or some other cardiodynamic event are used to help complete or substantiate the analysis when necessary.

Two lag factors must be taken into account when making the projection from the carotid pulse wave to the EKY: (1) The passage of the carotid pulse wave from the neck through the recording apparatus takes 0.01 sec.; (2) Passage of the pulse wave from the root of the aorta to the carotid artery takes 0.01 to 0.03 sec. (ave. 0.013). This latter can be determined for any individual from the ascending aorta EKY and its simultaneously recorded carotid pulse wave. A third possible lag factor appears in some instances where movement of the ascending aorta follows that of the left ventricular wall by 0.01 to 0.02 sec., but this matter requires further study. In the average record, a total lag of 0.03 to 0.04 sec. is used when studying ventricular curves.

Figure 3 schematically illustrates the most common type of ventricular curve (A), with some normal variations (C, D, E). Using the carotid sphygmogram (B), the interpretation can be made in terms of the physiological phases of the cardiac cycle as defined by Wiggers and others.

*Isometric Contraction Phase (1-2):* During this phase the ventricle is a closed chamber undergoing no volumetric change. However, it is changing from an ellipsoidal to a more globular shape,<sup>22</sup> thus producing a positional change of the border. The direction of movement depends on the point at which the record is taken and on the balance of factors affecting the movement of the particular segment. It is usually a descending limb in the PA projection, but may be ascending or horizontal. At times it is not demarcated, but merges with the ejection limb. The duration of this phase, as determined on the EKY, approximates previous estimates of 0.04 to 0.06 sec.

*Ejection Phase (2-3):* Following the opening of the semilunar valves at point 2, the ventricular wall, in most instances, moves outward for approximately 0.02 to 0.03 sec. This is believed due to a positional shift of the border as the a-v septum starts toward the apex and the latter rotates. Then, at point "x", the medial movement due to decrease in ventricular volume predominates and the major ejection limb is inscribed as a rapidly descending complex. The early positional change may not be evident when it merges with the isometric contraction movement or other complexes as in

\* "Traceolene" paper as manufactured by the Transolene Company, Barrington, Illinois, has proved particularly suitable for this purpose.

figures 3-D and E. The terminal portion of the ejection wave slopes more gradually and its end point is not definite in all curves. It is of interest to note that Wiggers<sup>21</sup> has observed a peak similar to that marked "x" in volumetric curves, which he called an "accidental" wave. In our records it appears to represent a shift in balance between positional and volumetric factors affecting border movement.

*Protodiastolic Phase (3-4):* This is the least clearly demarcated phase of the cardiac cycle on an EKY. It is approximately 0.04 sec. in duration and is a slightly concave descending segment. Its onset usually merges smoothly

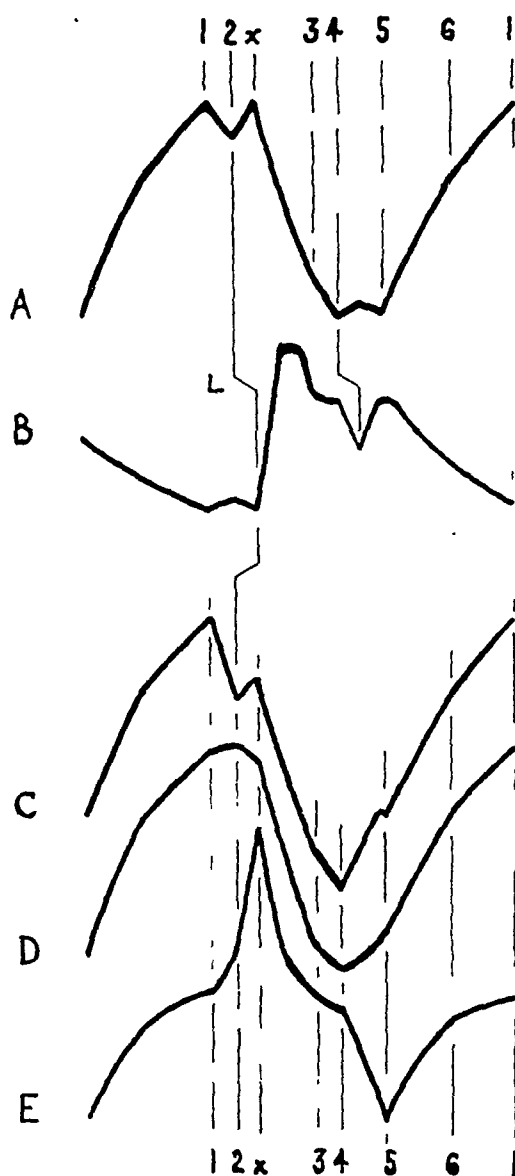


FIG. 3. Schematic drawing illustrating method of interpretation.

A, C, D, E—Variations of left ventricular electrokymograms, normal subjects. B—Carotid sphygmogram. L—Correction factor for lag of carotid recording system and pulse wave transmission time (see text). Vertical lines indicate phases of cardiac cycle.

with the terminal portion of the ejection limb, while its end point ordinarily is marked by abrupt angulation of the curve. Wiggers has identified this brief phase as that interval between the end of systolic ejection and the closure of the semi-lunar valves. As such, it is the first interval of diastole and does not refer to the same portion of the cardiac cycle as when the term is used clinically.

*Isometric Relaxation (4-5):* During this period the ventricles are again closed chambers and no volumetric change occurs. The complex which follows aortic valve closure at point 4, varies considerably. Commonly it resembles, and is opposite in direction to that of isometric contraction. It may be ascending (3C and D), biphasic (3A), or descending (3E). The latter is more common in the oblique projections. The movement is believed due to positional shifts of the ventricle as it returns to its resting state. Its duration varies from 0.06 to 0.16 sec.

*Ventricular Filling (5-6, 6-1):* The ventricle fills rapidly in early diastole producing a sharply ascending limb (5-6). With the decreasing rate of filling a change in slope occurs in later diastole (6-1). When the pulse rate is slow, evidence of auricular systole is occasionally seen. The duration of ventricular filling varies with pulse rate though no detailed studies of this relationship have been done.

Figure 4 shows examples of normal left ventricular curves comparable to those schematically shown in figure 3. In this and all subsequent examples, the upper record is the EKY, the lower is the carotid sphygmogram. Variations of A, B, and C are the usual curves of the middle and lower left ventricle in the posterior-anterior projection. While a certain type of curve may be most common in one segment of the heart, or in one projection, there is considerable variation. Such factors as the shape of the heart, height of the diaphragm, position of the patient, etc. affect the curves and account for patient to patient differences or differences on reexamination of the same patient. Records such as D are rarely obtained except in certain oblique projections.

The ventricular EKY appears to provide an opportunity for measuring, on a single curve, more phases of the cardiac cycle than has been previously possible. However, changes in direction or in steepness of slope of a limb do not always coincide with the onset of a specific event of the cardiac cycle; nor does the onset of a specific event always produce a definitely demarcated change in the EKY. The factors affecting border movement are so complex that the motion of any particular point on the heart border cannot be completely coördinated with events of the cardiac cycle. The EKY is a record of the net effect of all factors effecting transmission of x-ray.

A number of examinations have been made with the patient recumbent. Generally, they reveal a smoothing out of the entire curve so that it assumes a more trapezoid form (figure 5). The early systolic and diastolic changes are not so evident and the slow filling phase of diastole produces a horizontal or descending plateau. These differences appear due to the altered ana-

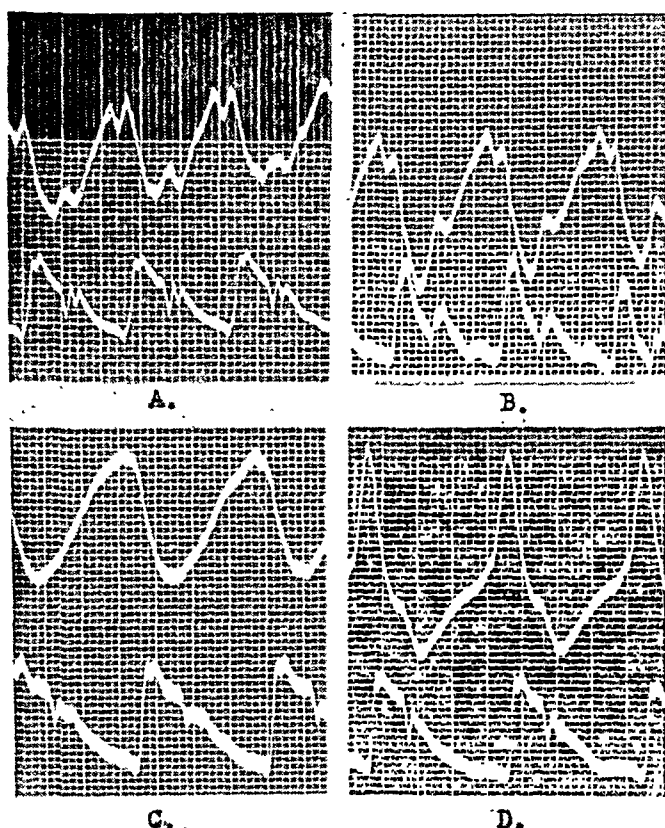


FIG. 4. Left ventricular electrokymograms showing variations in normal subjects.

In this, and subsequent illustrations, the upper curve is the EKY and the lower curve is the carotid sphygmogram.

A—PA projection, left lower border. B—Same projection, middle left border. C—LAO ( $20^\circ$ ), middle left border. D—LAO ( $60^\circ$ ), lower left border.

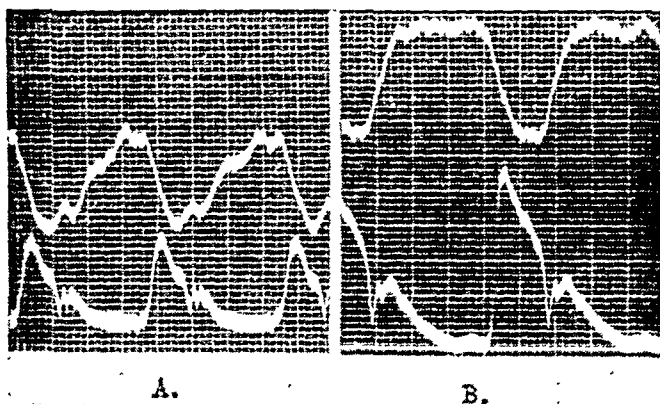


FIG. 5. A—EKY, middle left border, left ventricle (PA). Subject standing.  
B—Same with subject recumbent.

tomical relationship of the heart within the thorax, the slower heart rate and the increased ventricular filling which occur in the recumbent position. It has been noted that at rapid heart rates the ventricular curves may assume a more spiked contour.

It should also be noted that the highest and lowest points on the EKY do not necessarily represent the position of the border at the onset of systole and diastole. Though they represent the farthest lateral and medial movement of the ventricular wall, part of this movement may be due to positional change. This is well illustrated in figures 3E and 4D, where the highest peak occurs well after the onset of systole and the lowest peak after the onset of diastole, i.e. at the end of isometric ventricular relaxation.

### ATRIAL ELECTROKYMOGRAMS

Each cycle of the EKY taken from the areas of the atriae, usually consists of a basic pattern of two or three waves (figures 6 and 7). Considerable variation can occur in their details. Many resemble jugular phlebograms, but the same interpretation cannot be applied to both because they result from different mechanical factors. The atrial wall may move as a result of intrinsic atrial activity, because of transmitted motion from adjacent structures, or as part of a movement of the heart as a whole. Since the atriae are thin-walled and relatively inactive chambers riding on vigorously active ventricles, transmitted motions from the latter or from adjacent

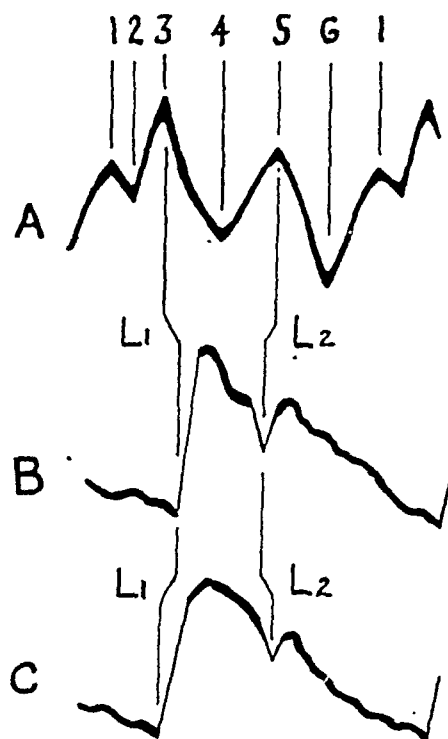


FIG. 6. Schematic basis for interpretation, right atrial EKY.

A—EKY, right atrium (mid position, PA). B—Carotid sphygmogram. C—EKY, pulmonary artery. Two steps: (1) comparison pulmonary and carotid artery, (2) comparison carotid to right atrium.  $L_1$  and  $L_2$  indicate time differences between opening and closing of semi-lunar valves on carotid and pulmonary artery records. For further detail see text.

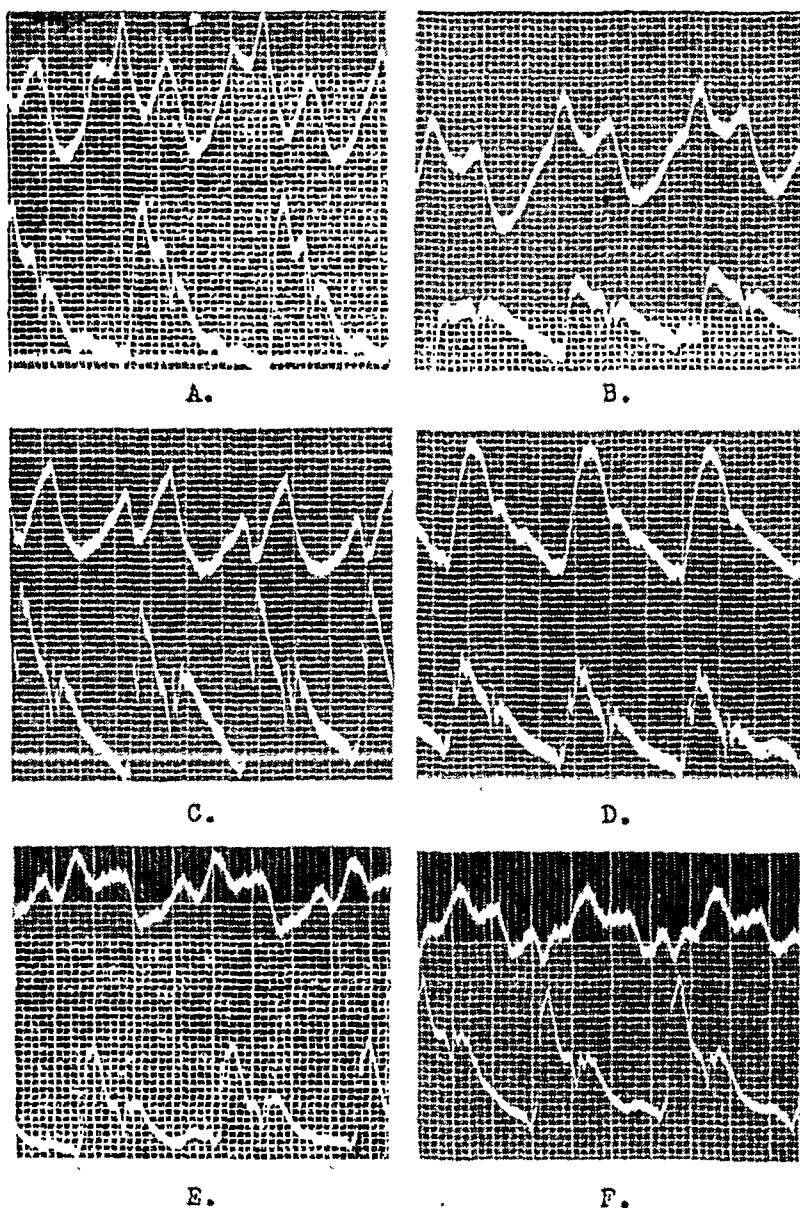


FIG. 7. Atrial electrokymograms illustrating variations in normal subjects.

A, B, C—Right atrium, PA projection. D—Pulmonary artery EKY, subject C, for correlation. E, F—Left atrium, RAO and LAO respectively.

arteries may dominate the curve. The effect of these and other physiological factors may vary from patient to patient, on the right and left atrium, or on different segments of the same atrium. For example, a recording from the right atrium close to the cardio-phrenic angle, may show predominately ventricular type movements; near the middle of this chamber silhouette, the ventricular effects are less marked and more evidence of intrinsic atrial activity may be seen; along the upper segment, the movements of the ascending aorta and/or superior vena cava may modify the curve. These varying influences may produce changes in contour of the record which mask or

modify those produced by the events of the atrial cycle. Each record must be individually analyzed as to what factors produce any specific movement. The superimposition of transparent tracings from different chambers is very helpful in this analysis.

For routine purposes, the carotid sphygmogram is preferred as a basis for interpretation of atrial curves. The right atrial EKY, however, cannot be directly compared with the carotid curve, since similar events on the two sides of the heart are not always synchronous. Therefore, the pulmonary artery EKY is utilized as shown in figure 6. The atrial and pulmonary artery electrokymograms are obtained separately in ordinary work. The simultaneously recorded carotid sphygmogram serves as a common time reference curve. The first step in interpretation is (a) the determination of the interval between the onset of the ejection wave on the carotid sphygmogram and that on the pulmonary artery EKY ( $L_1$  of figure 6); and (b) the determination of the interval between the nadir of the incisura of these two records ( $L_2$ ). Step two is the application of these relationships to the atrial curve. On figure 6,  $L_1$  and  $L_2$  are shown of differing duration and direction. The time relationship between the onset of the ejection wave on the carotid sphygmogram and that on the pulmonary artery EKY is not necessarily the same as the relationship between the incisura on the two curves since the duration of ejection from right and left ventricle may vary (Katz).<sup>28</sup> The right atrial and the pulmonary artery electrokymograms can be recorded simultaneously, but this requires additional special apparatus. The interpretation of the right atrial EKY, shown in curve A, figure 6, can be made as follows:

1-2: This first negative limb represents movement of the atrial wall toward the mid-line and is associated with atrial systole. In the two-waved atrial curves (figures 7, B and C), it may be absent or may be evident only as a poorly defined change in contour.

2-3: The first positive wave represents an outward movement associated with early ventricular systole and related to a-v valve closure. It is probably due in most instances to pressure or positional changes transmitted from the ventricle during its isometric contraction phase. It is present on both two and three-waved curves.

3-4: The second negative wave is associated with ventricular ejection and is believed due to the descent of the atrio-ventricular septum toward the apex. This pulls the atrial wall sharply toward the mid-line; at the same time the atrium rides inward on the ventricle as the latter becomes smaller. In most cases point 3 corresponds to point "x" of the ventricular record (figure 3). In some instances ventricular ejection begins at point 3. The wave may then descend to the baseline or only a short way, dependent upon the degree of ventricular effect on the curve.

4-5: The second positive wave begins at about the middle of the ventricular ejection period. Apparently at point 4, atrial filling becomes the

dominant factor and produces an outward movement despite the fact that the ventricle is still getting smaller. The V or L-shaped complex, 3-5, is quite consistently present and is often the largest complex of the right atrial EKY.

5-6: The third negative limb begins with the closure of the semi-lunar valves at 5 and ends with the opening of the a-v valves at 6. This movement is believed due to a positional shift of the heart as a whole. This can be shown in some cases by comparing movement of right and left heart borders. The depth of this limb varies, but it is clearly present in most records. Its duration is the same as that of the isometric ventricular relaxation phase as measured on the ventricular EKY. In some instances the complexes from 4 to 1 bear a different time relationship to the incisura of the arterial curves so that the semi-lunar valves appear to close between 4 and 5, and the a-v valves open at point 5. In such cases, the identification and interpretation of these complexes varies from that of the usual curve just described.

6-1: The third and final limb is correlated with the onset of ventricular filling. It might be expected that the atrial wall would move inward as blood passes from atrium to ventricle. During this period, however, the atrium rides outward on the expanding ventricle and apparently the column of blood in atrium and vein moves "en masse" so that very little intrinsic movement of the atrial wall occurs until its systole begins.

Right atrial curves were easily obtained in most subjects at approximately the middle of the right lower arc of the heart, with the subject erect and in the PA projection. Occasionally the right ventricle formed this segment of the silhouette. In the recumbent position, a predominately arterial or ventricular type wave was usually seen in this area.

The carotid sphygmogram is used directly to aid in the interpretation of the left atrial EKY. Referring to figure 6 and figure 7F, the movements of the left atrium between points 1 and 4 are similar to the movements of the right atrium. Between points 4 and 1, the curves usually differ, in that on the left atrium the semi-lunar valves appear to close between 4 and 5, while the a-v valves open at point 5. Phillips,\* and Luisada,<sup>19</sup> using the stethogram for orientation, reached a similar interpretation. In our experience it has been hard to obtain "pure" left atrial electrokymograms in normal subjects. It is difficult to be certain that this chamber is in silhouette and to visualize it free from adjacent structures in the various oblique projections. Even when the silhouette seems well visualized, the curves obtained often show predominantly ventricular, arterial or "mixed" characteristics.

In summary, it is emphasized that factors affecting atrial border movement are quite complex and at the moment we feel much as F. Roberts,<sup>24</sup> that the atria, to a great extent, are passengers in the movements of the ventricles, making it difficult to distinguish between active and passive atrial movement.

\* Personal communication from Dr. Edward Phillips, Peter Bent Brigham Hospital, Boston, Massachusetts.



## ARTERIAL ELECTROKYMOGRAMS

Electrokymograms from the pulmonary artery, ascending aorta and aortic knob closely resemble the carotid sphygmogram (figure 8). They can be described with reference to the phases of the ventricular cycle.

The onset of ventricular systole (isometric contraction) is usually not reflected in any clear cut change on the arterial EKY. In some instances, a small wave, either negative or positive, appears 0.04 to 0.06 sec. ahead of the major upward limb. Such a "preëjection" complex, when present, is probably due to positional change of the vessel or pressure change transmitted through the semi-lunar valves, occurring as the ventricle alters shape and intra-ventricular pressure increases during isometric contraction.

The onset of ventricular ejection results in a sharp upward movement of the tracing which reaches its peak near mid-systole. As ejection pro-

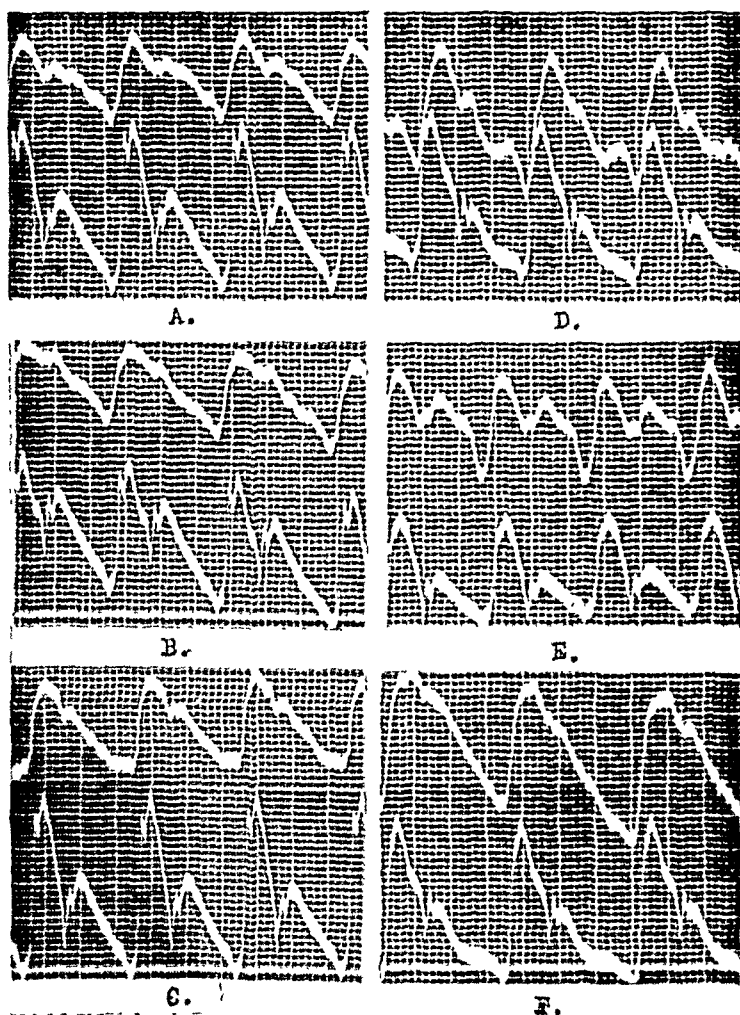


FIG. 8. Arterial electrokymograms, normal subjects.

A, B, C—Pulmonary artery, ascending aorta, and aortic knob, subject N. H. D, E, F—Pulmonary artery, ascending and aortic knob, subject J. S.

ceeds, a descending limb of lesser slope is inscribed. The end of the ventricular ejection phase is marked by a break in contour, or an incisura on the descending limb though not as definitely as on the carotid sphygmogram. The protodiastolic phase of ventricular activity is also not always clearly defined. The onset of ventricular diastole (isometric relaxation) is marked by a small upright wave which gives way to a gradually falling slope. This may be smooth in its descent or may show irregular undulations and peaks.

Electrokymograms from the aortic knob generally show an abrupt, steep, rising limb, a peaked contour, an "incisura" at a high level above the baseline, and a descending limb of lesser slope. In comparison with this, the pulmonary artery curves tend to show rising and falling limbs of more equal slope, a more rounded contour and "incisura" falling closer to the baseline. The electrokymograms of the ascending aorta are variable in appearance and in many instances show a large secondary wave after the incisura, figure 8E. This appears related to superior vena cava activity and probably represents an "impure" curve with both ascending aorta and superior vena cava in the recording aperture. Variations from these generalities are common so that it is not possible to identify a curve as pulmonary artery, ascending aorta, or aortic knob from its appearance alone. From rough comparisons, aortic curves appear of greater amplitude than pulmonary artery records, though standardization of height is not possible at present.

The technic of obtaining these records varies with the individual patient. In normal young adults it is easy to record the aortic knob movement in the posterior-anterior projection. Occasionally the knob may be inconspicuous and a slight degree of rotation may be needed to bring it out. The pulmonary artery tracings are usually obtained in the posterior-anterior projection, though at times it is necessary to rotate the subject into the right anterior oblique position. This is especially true in subjects with a transverse type heart. Electro-kymograms of the ascending aorta are taken close to the point of origin of the vessel and are most easily obtained with the subject in the LAO position. The optimum degree of rotation varies. As indicated before, the right border of the ascending aorta cannot always be thrown into silhouette free from the superior vena cava and the spine shadows. We have had difficulty in visualizing and recording the movement of the descending aorta below the aortic knob. Among subjects over 60 years of age, satisfactory arterial curves have not been obtained as easily as in younger subjects. A dilated or tortuous descending aorta or enlarged left ventricle, for example, may interfere with visualization of the pulmonary artery. Where, as in older subjects, the descending aorta forms a distinctly visible arc to the left of the spine its movements can usually be recorded. For movement to be recorded in this area, it appears that (a) the density of the vessel must be increased so as to give contrast with surrounding structures; (b) the vessel must be curved enough so that the passage of the pulse wave can produce a positional shift. Our work so far leads to the belief

that the recorded movements of the great vessels are due more to straightening and positional shifts of the vessel associated with the passage of the pulse wave, than to true expansile pulsation.

A number of interesting and valuable measurements have been made from the arterial electrokymograms recorded simultaneously with the carotid sphygmogram. One of our first applications has been to study the synchronism or asynchronism of ventricular ejection in normal subjects, and in patients with bundle-branch block.<sup>17</sup> The method is based on the determination of the time interval between the onset of the ejection wave on the pulmonary artery EKY and that of the ascending aorta EKY. For practical purposes, this indicates the time of onset of ejection of blood from the right ventricle relative to that from the left ventricle. This time can be determined by recording pulmonary artery and ascending aorta separately, each with a simultaneous carotid sphygmogram, then using the latter as a common time reference curve to compare pulmonary artery and ascending aorta. The electrokymograms of the pulmonary artery and ascending aorta can also be recorded simultaneously. This is more difficult and time consuming and requires a special multiple channel instrument.

TABLE I

AAc		AKc		AAc to AKc Difference		PAc		PAc to AAc Difference	
Sec.	No. Subj.	Sec.	No. Subj.	Sec.	No. Subj.	Sec.	No. Subj.	Sec.	No. Subj.
.00	9	.01	21	.03	5	.03	16	.03	2
.01	34	.00	46	.02	26	.02	20	.02	6
.02	19	-.01	31	.01	28	.01	32	.01	13
.03	6			.00	8	.00	14	.00	14
						-.01	18	-.01	19
								-.02	11
								-.03	3
Aver. .013		.01 to -.01		.014		.03 to -.01		.03 to -.03	
Total Subj.	68		98		67		100		68

The measurements studied to date are listed in table 1. AAc, PAc, and AKc denote the interval between the onset of ejection on the ascending aorta, pulmonary artery, and aortic knob electrokymograms and the onset of ejection on the simultaneously recorded carotid sphygmogram.

*Column 1:* The AAc measurement indicates the pulse wave transmission time between the ascending aorta and the carotid. In the normal young subjects it ranged from 0.00 to 0.03 sec. (average 0.013). It is probable that the 0.00 readings actually represent values between that figure and 0.01 sec. since the method is accurate only within 0.01 sec. In addition, positional shifts of the aorta may occur with ventricular activities and obscure or alter the apparent take-off point of the aortic ejection wave.

*Column II:* The AKc measurement indicates the difference in the time of arrival of the pulse wave at the aortic knob and the carotid artery. It varies from  $+0.01$  sec. to  $-0.01$  sec., i.e. the onset of "ejection" on the aortic knob EKY may coincide with, or may precede or follow that on the carotid sphygmogram by as much as 0.01 sec. This variation can be explained by (1) differences in the distance from the left ventricle to the two points of recording; (2) differences in rate of pulse wave transmission from the aorta to the points of recording. A preliminary study of a large group of older men, most of whom had some degree of aortic arteriosclerosis with elongation and tortuosity, has shown a significant number of subjects in whom the aortic knob ejection point occurs as much as 0.05 sec. after the carotid ejection point.

*Column III:* AAc to AKc difference. This measurement indicates the time for transmission of the pulse wave from the ascending aorta to the aortic knob. It varied from 0.00 to 0.03 sec. (average 0.014 sec.). Again the 0.00 readings probably represent values between that figure and 0.01 sec. This value is prolonged in many older subjects.

In the living subject the distance from the point of recording on the ascending aorta to that point visualized as the "aortic knob" is variable. It can be estimated at 8 to 10 cm. from measurements given in anatomy text books.<sup>25</sup> Assuming that AAc to AKc times of 0.00 are actually 0.01 sec., the transmission time from the ascending aorta to the aortic knob becomes 0.01 to 0.03 sec. Then the pulse wave transmission rates in the aorta would be from 3 to 10 meters per second. This closely approximates prior estimates.<sup>26</sup>

*Column IV:* The PAc measurement indicates the difference in the time of onset of the ejection waves on the pulmonary artery EKY and that on the carotid sphygmogram. It serves to compare right and left heart events. It varied from  $+0.03$  to  $-0.01$  sec., i.e. pulmonary artery ejection might precede carotid ejection by as much as 0.03 sec., or follow it by as much as 0.01 sec. The range of the PAc measurement is sufficiently narrow and constant that unusual variations can be considered as indicative of abnormal degrees of ventricular asynchronism. In a large group of normal adults all measurements were between  $+0.03$  and  $-0.01$ . In 15 of 16 patients with bundle-branch block, measurements were significantly outside this range (LBBB 0.04 to 0.07 and RBBB  $-0.04$  to  $-0.05$  sec.).<sup>17</sup> Since this previous communication, we have examined a group of subjects over age 60, and to date their PAc measurements have corresponded to those of the younger age group except in two of 30 cases. One of the exceptions had a dilated descending aorta which may have been superimposed on the pulmonary artery.

*Column V:* PAc to AAc difference. This measurement can be used to determine the actual degree of asynchronism of ejection from right and left ventricles.<sup>17</sup> In normal subjects it was found that the PAc to AAc difference equals  $+0.03$  to  $-0.03$  sec., i.e. the ejection on the pulmonary artery EKY

might precede or follow that on the ascending aorta by 0.03 sec. Stated differently, ejection from either ventricle may precede that from the other by as much as 0.03 sec. In a group of 68 normal subjects left ventricular ejection led in 33 cases; right ventricular ejection led in 21 cases; ejection was synchronous in 14 cases. On reexamination of a number of these subjects, the PAc and AAe times were found in the same range, and individual measurements, with rare exception, were within 0.01 sec. of the original. This resulted, in an occasional case, in a change of the degree or side of asynchronism. We have observed this same phenomenon of changing asynchronism while making a continuous recording as a subject held his breath for a long period. Thus far, we have found PAc to AAe differences greater than 0.03 sec. only in subjects with electrocardiographic evidence of bundle-branch block. The results in the normal group differ from those of Luisada and Fleischner<sup>20</sup> who found, in eight cases, that right ventricular ejection always led.

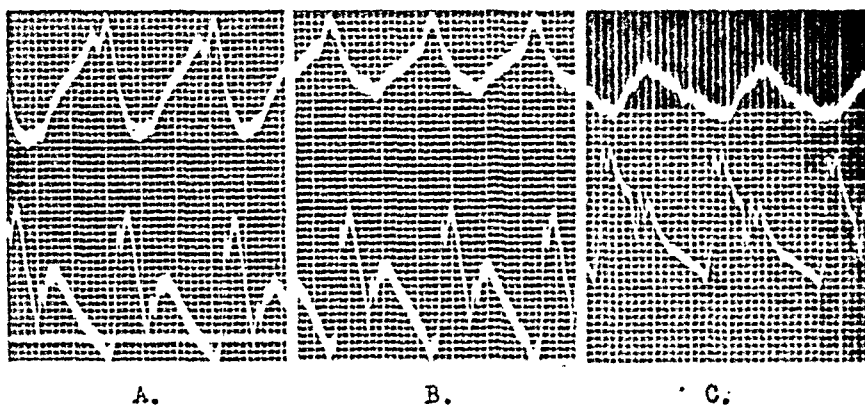


FIG. 9. Miscellaneous electrokymograms.

A—Left ventricle, middle left border (PA). B—Density, same subject, taken 2 cm. medial from border. C—Density curve from right lower lung, normal subject.

These measurements are accurate within about 0.01 sec. We have recorded simultaneously from similar levels on right and left carotid arteries, and find no difference in timing of the complexes, so that either vessel can be used for electrokymographic work. It would be expected that pulse wave transmission time in these vessels would vary with changes in blood pressure, pulse pressure, etc. Under the conditions of our examination, no appreciable change in these factors was noted, except for lessening of tachycardia in some excitable subjects as the examination progressed. In some instances blood pressures were taken before, during and after the examination. Such changes as appeared did not alter the blood pressure beyond the normal range and the various electrokymographic measurements were not significantly changed. The effects of greater pulse rate and blood pressure variations on electrokymographic measurements are in process of study.

EKY - Left Ventricle  
Upper Left Border

EKY - Left Ventricle  
Middle Left Border

Carotid-Sphygmogram

ECG - Lead II

Stethogram - Apex

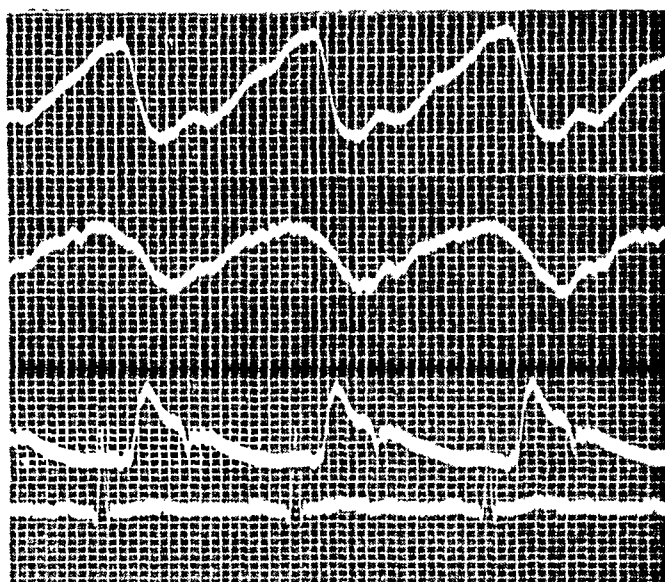
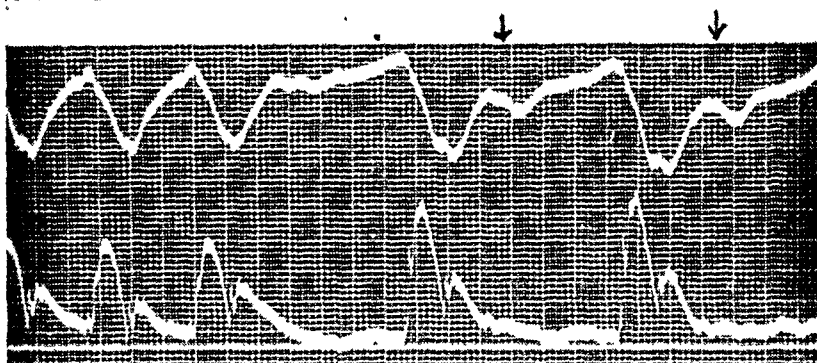
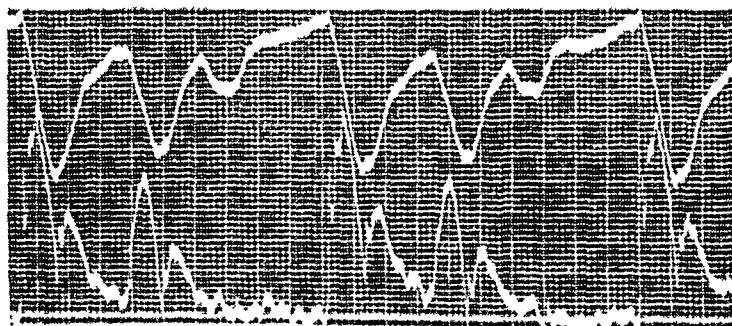


FIG. 10. Sample of simultaneous recording of multiple events.



A.



B.

FIG. 11. Ventricular premature contractions.

Noted clinically and on ECG of subject with no other sign of heart disease. A—Lower left ventricle (PA). Normal rhythm changing to bigeminal. Arrow marks premature contraction which bulges, but fails to open semi-lunar valves. B—Period of trigeminal rhythm, same subject.

Another interesting measurement is that from the onset of the ejection limb on an arterial curve to the incisura, i.e. from opening to closing of the semi-lunar valves. This indicates the effective ejection phase of the ventricle (including protodiastole). Partially studied data indicate that the duration of ejection can be different in the right and left ventricles of man, and is often longer on the right. Katz demonstrated this same phenomenon in animals.<sup>23</sup>

### OTHER ELECTROKYMGRAMS

The EKY is being used to obtain records of such events as heart "density" changes, hilar shadow movements, pulmonary vascular flow, etc. For ex-

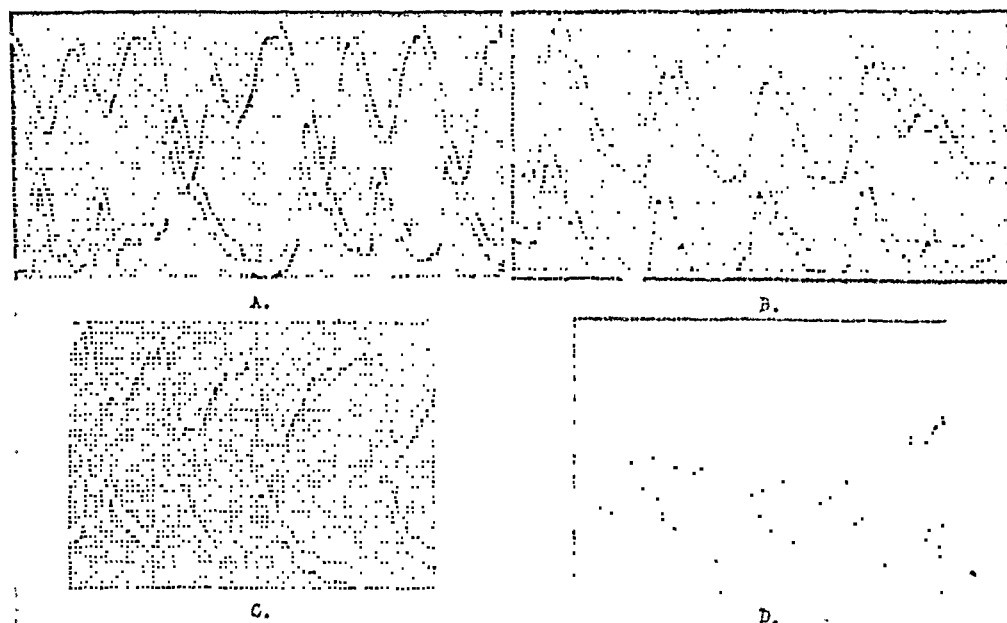


FIG. 12. Auricular fibrillation.

Two subjects with arteriosclerotic and hypertensive heart disease and enlarged hearts. A—Middle left ventricle (LAO-10°). Complexes irregular in rate, rhythm, amplitude and contour. B—Same subject. Pulmonary artery (PA). C—Second subject. Lower left ventricle (PA). Splintering and irregularity of complexes. D—Same subject. Right atrium (PA).

ample, by placing the aperture of the instrument over the body of the ventricle, a record is obtained which resembles the volumetric curve of the ventricle. While similar to the ventricular border curve, it tends to show less effect from positional shift of the heart (figure 9). Such a "density" curve reflects changes occurring with variations in the amount of blood within the heart and alterations in the posterior-anterior thickness of the heart muscle. If the heart was a sphere which expanded and contracted uniformly about the center point at which the electrokymograph was focused, the density change could be used to accurately estimate cardiac output. Actually, the heart is of relatively irregular shape and undergoes mass positional shifts,

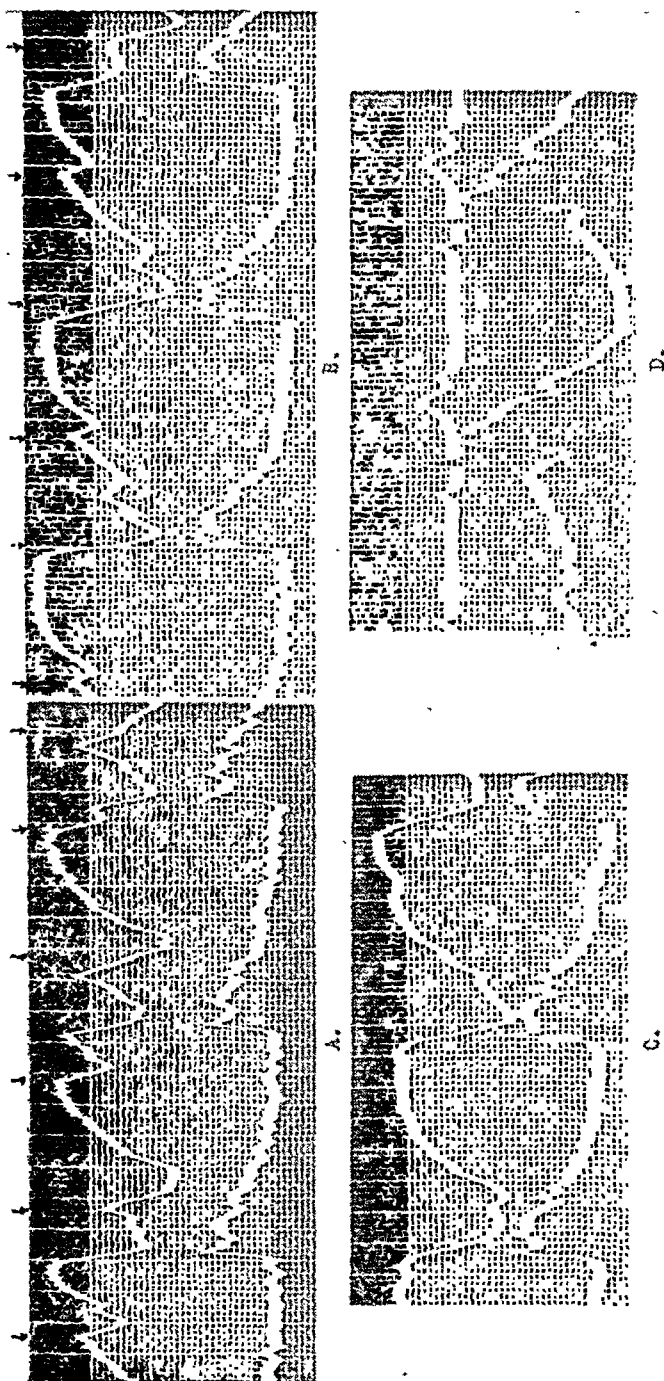


FIG. 13. Complete atrio-ventricular dissociation in subject with calcification annulus fibrosis, etiology unknown. No other signs of cardiovascular disease.

A—Left atrium (RAO). Recurrent descending limbs (arrow) associated with atrial contraction. Effect of ventricular systole evident at about one-half rate of atrium. B—Right atrium (PA). C—Middle left ventricle (PA). Large complexes associated with slow rate and prolonged diastole. D—Electrocardiogram and carotid sphygmogram.



so that the central beam of the x-ray is passing through different thicknesses and areas of heart and blood as the heart moves in its cycle. Nevertheless, investigations are being made with simultaneously recorded ballistocardiogram and EKY to see if some correlation can be shown between these "density" curves and cardiac output.

Mixed-type waves can be recorded from the superior and inferior vena cava. These tracings resemble phlebograms, but superimposed movements

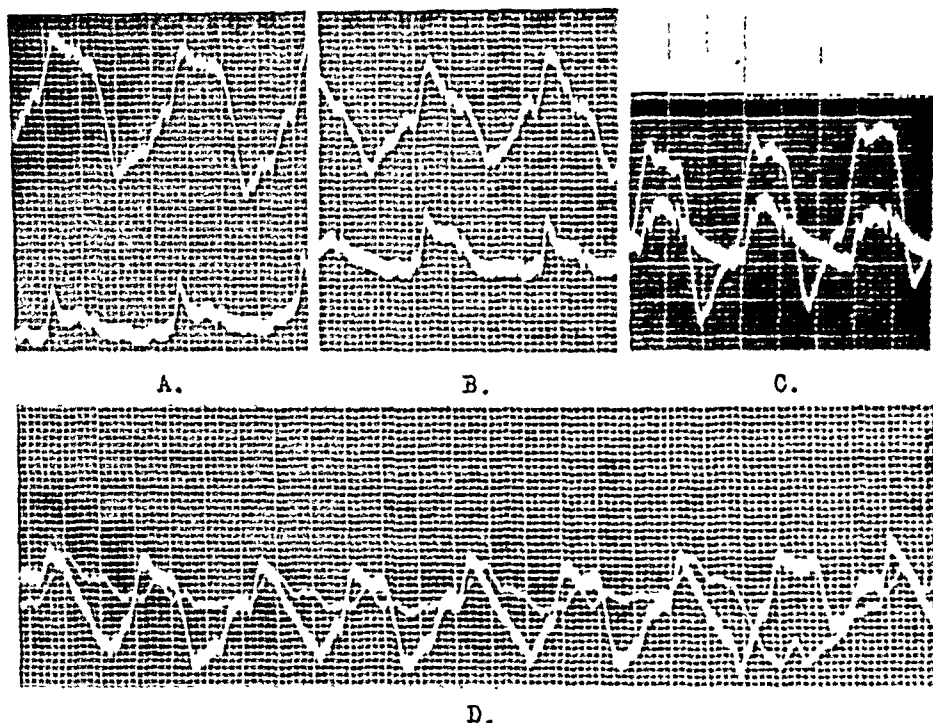
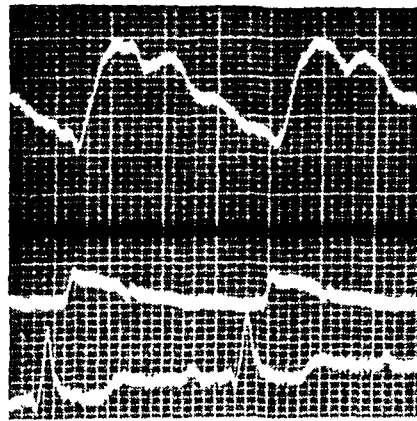


FIG. 14. A and B—Myocardial infarction.

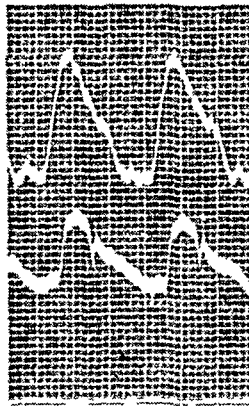
Subject with hypertensive heart disease, enlarged heart and old posterior infarct. Left lower border PA and LAO respectively. Paradoxical motion evident. Outward movement in early systole. Slowly descending plateau as ejection proceeds. Diastolic collapse with inward movement during isometric ventricular relaxation. C—Malignant hypertension with enlarged heart and electrocardiographic evidence of left ventricular hypertrophy. No signs or symptoms of infarction. Paradoxical motion, lower left ventricle (LAO). D—Pulsus alternans in subject with hypertensive and arteriosclerotic heart disease, enlarged heart and old anterior infarction. Middle left ventricle (PA). Note paradoxical movement on all curves with alternating contour of complexes.

of arteries and heart may complicate their interpretation. Arterial type recordings have been obtained from the hilar shadows and the peripheral lung fields (figure 9C). This makes it possible to study pulmonary circulation. The device has also been modified for use as a photo-electric plethysmograph,<sup>10</sup> to record diaphragm movements, and work is in progress to adapt it as a recorder for the ballistocardiograph.

Figure 10 illustrates the simultaneous recording of several events by the special multiple channel instrument to which we have previously referred.



A.

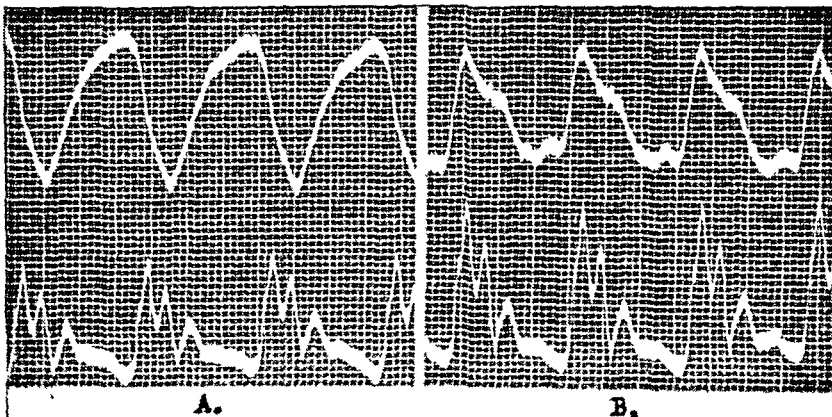


B.

FIG. 15. Bundle-branch block.

Subjects with arteriosclerotic heart disease and classical electrocardiographic evidence of bundle-branch block.

A—Right bundle-branch block. Ejection on pulmonary artery EKY (upper) 0.05 sec. behind that on carotid (middle), i.e.  $P_{Ac} = -0.05$  sec. Lower curve ECG—Lead II. B—Left bundle-branch block. Ejection on pulmonary artery (upper) 0.07 sec. ahead of carotid (lower), i.e.  $P_{Ac} \approx 0.07$  sec. These are significant variations from normal  $P_{Ac} + 0.03$  to  $-0.01$  sec.<sup>17</sup>



A.

B.

FIG. 16. Aortic regurgitation—subject with luetic aortitis and enlarged left ventricle. A—Middle left ventricle (RAO). Ascending and descending limbs from V-shaped trough with absence of complexes associated with isometric contraction and isometric relaxation on all views. Carotid sphygmogram shows systolic collapse. B—Ascending aorta, note absence of incisura.

## THE ELECTROKYMOGRAPH IN CARDIOVASCULAR DISEASE

The primary effort of this group, aside from development of the instrument, has been to study the normal EKY and its variations, especially the ventricular records. A limited number of observations has been made on subjects with cardiovascular disease. A great amount of work must still be done before any attempt to define the "normal" or "pathological" EKY can be made. The following records, figures 11, 12, 13, 14, 15 and 16, are presented, not as pathognomonic EKY patterns, but to demonstrate some of the changes we have noted in the presence of cardiovascular disease and to point out some of the many possible applications of the instrument.

## DISCUSSION

The development of the electrokymograph provides an improved method for graphically recording the movements of the borders of the heart and great vessels. Devices used for this purpose in the past have been of limited value because of such factors as difficulties in interpretation and inability to easily record some simultaneous cardio-dynamic event. The instrument has proved a valuable tool in the field of cardiovascular physiology. The simultaneous recording of electrokymograms, sphygmograms, stethograms, etc. should lead to a better understanding of the relationships of movements and pressure changes, of mechanical and electrical events, and to a reevaluation of many phases of cardiovascular activity.<sup>27, 28</sup>

The value of the instrument in clinical work remains to be defined. Promising results have been obtained in preliminary studies of the arrhythmias and myocardial infarcts such as presented here. It is of interest to note the striking similarity between the ventricular EKY found in some human subjects with myocardial infarcts (figure 14) and the ventricular myogram obtained by Tennant and Wiggers,<sup>29</sup> after they produced experimental infarction in dogs. Both demonstrate clearly "paradoxical" movement of the infarcted ventricular wall. In examinations being done on a large group of older men, we have encountered several instances of paradoxical type movement in subjects with no, or minimal, cardiovascular symptoms and a normal ECG. Records from subjects with valvular heart lesions have been difficult to analyze. It may be as Stumpf<sup>4</sup> said concerning roentgenkymography that the forces involved in the movement of the wall of a chamber in the presence of a valvular lesion are too complicated to permit prediction from theoretical considerations. We have used the instrument to study the movements of aortic aneurysms and mediastinal masses, though no records have been presented. One case diagnosed aneurysm, and another diagnosed tumor, have been verified at surgery and by response to x-ray therapy respectively. As stated before, we have done only a few preliminary studies of cardiovascular disease. It remains to be determined

in what specific types of cardiovascular disease pathognomonic EKY patterns appear and just what clinical value the instrument will have.\*

### CONCLUSIONS

1. The principles of the electrokymograph, the technic of its application and method of interpreting the records have been presented.
2. Electrograms from normal subjects and from selected subjects with cardiovascular disease have been demonstrated.
3. The instrument provides a valuable aid for studying the physiology of the cardiovascular system in human subjects and it warrants continuing evaluation of its possible clinical application.

### BIBLIOGRAPHY

1. CHAMBERLAIN, W. E., and DOCK, W.: The study of the heart action with the roentgen cinematography, *Radium*, 1926, vii, 185.
2. HIRSCH, I. S.: The recording of cardiac movements and sounds by the roentgen ray (kymophonoroentgenography), *Radium*, 1934, xxii, 403.
3. HIRSCH, I. S.: The application of kymoroentgenography to the diagnosis of cardiac disease, *Radium*, 1934, xxii, 720.
4. STUMPF, PL., WEBER, H. H., and WELTZ, G. A.: Roentgenkymographische Bewegungslehre innerer Organe, Leipzig, Thieme, 1936.
5. HECKMAN, K.: Moderne Methoden zur Untersuchung der Herzpulsation mittels Roentgenstrahlen, *Ergebn. inn. Med.*, 1937, lii, 569.
6. MARCHAL, M.: The registration of pulsations of the lung parenchyma and the cardiovascular system by kine-densigraphy, *Arch. d. mal. du coeur*, 1946, xxxix, 345.
7. HJELMAR, GUNNAR: The registration of the movements of the heart with Geiger-Mueller counter and synchronous electrocardiography, *Acta Radiologica*, 1946, xxvii, 334.
8. HENNY, G. C., and BOONE, B. R.: Electrograms for recording heart motion utilizing the roentgenoscope, *Am. Jr. Roentgenol. and Rad. Therapy*, 1945, liv, 217.
9. HENNY, G. C., and BOONE, B. R.: Electrograms for recording heart motion, improved type, *Am. Jr. Roentgenol.*, 1947, lvii, 409.
10. GILICK, F. G., BOONE, B. R., HENNY, G. C., and OPPENHEIMER, M. J.: The electrograms: application as a photo-electric plethysmograph, *Fed. Proc.*, 1946, Part II, 33.
11. HENNY, G. C., BOONE, B. R., and CHAMBERLAIN, W. E.: The electrograms: an apparatus for recording motion (for example, that of the heart border shadow), *Fed. Proc.*, 1946, Part II, 44.
12. BOONE, B. R., GILICK, F. G., CHAMBERLAIN, W. E., and OPPENHEIMER, M. J.: Electrograms of heart border motions: principles of record interpretation, *Fed. Proc.*, 1946, Part II, 9.
13. CHAMBERLAIN, W. E., BOONE, B. R., ELLINGER, G. F., HENNY, G. C., and OPPENHEIMER, M. J.: Asynchronism of ejection of the ventricles as measured with the electrograms, *Fed. Proc.*, 1947, vi, 88.
14. BOONE, B. R.: Application of the electrograms to the study of cardiovascular physiology, *Abstracts of Communications, XVII International Physiological Congress*, 5.

\* Since this paper was submitted, additional papers on the clinical application of electrograms have been published or have been accepted for publication. References to this material have been added.<sup>30, 31, 32, 33, 34</sup>

15. HENNY, G. C.: Electrokymograph: apparatus for recording cardiovascular phenomena utilizing the roentgenoscope, Abstracts of Communications, XVII International Physiological Congress, 5.
16. BOONE, B. R., CHAMBERLAIN, W. E., GILICK, F. G., HENNY, G. C., and OPPENHEIMER, M. J.: Interpreting the electrokymogram of heart and great vessel motion, *Am. Heart Jr.*, 1947, xxxiv, 560.
17. ELLINGER, G. F., GILICK, F. G., BOONE, B. R., and CHAMBERLAIN, W. E.: Electrokymographic studies of asynchronism from the ventricles: normal subjects and patients with bundle-branch block (accepted for publication, *Am. Heart Jr.*).
18. CHAMBERLAIN, W. E.: Roentgen electrokymography, *Acta Radiol.*, 1947, xxviii, 847.
19. LUISADA, A. A., FLEISCHNER, F. G., and RAPPAPORT, E. E.: Fluorocardiography (electrokymography), I. Technical aspects, II. Observations on normal subjects, *Am. Heart Jr.*, 1948, xxxv, 336.
20. LUISADA, A. A., and FLEISCHNER, F. G.: Temporal relation between contraction of right and left sides of the normal human heart, *Proc. Soc. Exper. Med. and Biol.*, 1947, lxxvi, 436.
21. WIGGERS, C. J.: Circulation in health and disease, 1923, 2nd Ed., 93 and 94.
22. ROESLER, HUGO: Clinical roentgenology of the cardiovascular system, 1943, 2nd Ed., 111.
23. KATZ, L. N.: Asynchronism of right and left ventricles, *Am. Jr. Physiol.*, 1925, lxxii, 655-681.
24. ROBERTS, F.: The limitations of kymography, *British Jr. Radiol.*, 1939, xii, 638-644.
25. MORRIS: Human anatomy, 1947, 10th Ed., 605-607.
26. HAMILTON, W. F.: Textbook of human physiology, 1947, 310.
27. SUSSMAN, M. L.: A physiologic approach to cardiovascular roentgenology, *Minn. Med.*, 1947, xxx, 1041-1048.
28. STAUFFER, H. M.: Electrokymography, Staff Meet. Bull. Hosp. Univ. Minn., 1947, xviii, 462-473.
29. TENNANT, R., and WIGGERS, C. J.: The effect of coronary occlusion on myocardial contraction, *Am. Jr. Physiol.*, 1935, xcii, 351-361.
30. LUISADA, A. A., and FLEISCHNER, F. G.: Dynamics of the left auricle in mitral valve lesions, *Am. Jr. Med.*, 1948, iv, 791-797.
31. GILICK, F. G., and REYNOLDS, W. F.: Clinical application of electrokymography, *California Med.*, 1949, lxx, 1-6.
32. RANDAK, E. F., BOONE, B. R., ELLINGER, G. F., and OPPENHEIMER, M. J.: Ventricular isometric relaxation phase as measured on the electrokymogram, *Fed. Proc.*, 1948, vii, No. 1.
33. BOONE, B. R., RANDAK, E. F., ELLINGER, G. F., and OPPENHEIMER, M. J.: Electrokymographic studies of the ventricular isometric relaxation phase of the cardiac cycle in man, *Jr. Applied Physiol.*, 1949, i, 534-544.
34. RING, G. C., BALABAN, MIRIAM, and OPPENHEIMER, M. J.: Measurements of heart output by electrokymography, *Am. Jr. Physiol.*, 1949, clvii, 343.

# SECONDARY AMYLOIDOSIS IN SPINAL CORD INJURY \*

By CHARLES EDWARD THOMPSON, M.D., F.A.C.P., *Chicago, Illinois*, and  
MARION LEE RICE, JR., M.D., *Memphis, Tennessee*

RECENT reviews of the literature reveal an awakening of interest in the study of amyloidosis.<sup>1, 2, 3, 4, 5</sup> The occurrence of this lardaceous pathological process in relationship to spinal cord injury had not been noted previously, with the exception of a case reported in 1867 by Fagge.<sup>6</sup> A large number of spinal cord injuries, resulting from World War II, are under observation in Veterans Administration hospitals. Sufficient time has now elapsed for these patients to be subjected to the effects of wasting disease, tissue atrophy and repeated infections. Secondary amyloidosis in this group of patients then might be expected to occur.

The purpose of this manuscript is to report four cases of secondary amyloidosis found at autopsy in patients with spinal cord injury and to discuss the clinical significance of this process.

*Case 1.* This 22 year old white male was injured in a fall November 13, 1942. Following this injury a physiologically complete myelopathy at the level of D-4 was present. His course subsequent to this event was the usual one of decubitus ulcer and recurrent urinary infection with renal vesicular calculi. The patient maintained a poor state of nutrition throughout this time.

On March 28, 1947, he was admitted to this hospital for treatment and care of his spinal cord injury. At this time he was markedly undernourished and had multiple decubitus ulcers. His urinary status was as follows: suprapubic catheter, penoscrotal fistula, bilateral renal calculi and chronic cystitis. The following were the laboratory data: urine albumin 2 plus, no casts or cells in urine; red blood cells 3,400,000; hemoglobin 12 gm.; total protein 6.5 with A/G ratio 1.5. X-ray pyelography revealed nonfunction of left kidney and small multiple calculi in right kidney.

*Course in Hospital:* A high protein, caloric and vitamin diet was instituted with improvement of ulcers but only slight nutritional response. Gross hematuria developed in July. Slight rectal bleeding occurred in September. Proctoscopic examination on September 10, 1948, revealed edema and injection of the mucosa. The patient suddenly became nauseated and oliguria appeared. Blood pressure at this time was 50 mm. of mercury systolic and 30 mm. diastolic. Red blood cells 3,300,000, hemoglobin 9.2 gm., and non-protein nitrogen 56 mg. per cent. Cystoscopic examination revealed calculi had moved into the right ureter. An emergency right nephrotomy was performed to establish urine flow. There was no improvement in renal function from this procedure. Shock continued. On September 13, 1947, jaundice developed. The icteric index was 33, with no urobilin in feces or urine. On September 16, the non-protein nitrogen was 123 mg. per cent; the urine contained 4 plus albumin; the

\* Received for publication March 9, 1948.

From Paraplegia Service, Veterans Administration Medical Teaching Group, Kennedy Hospital, Memphis, Tennessee. Published with permission of Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

cephalin flocculation test was 4 plus. Oliguria and azotemia progressed, leading to death on September 20, 1947.

**Pathological Findings:** Autopsy examination revealed amyloid infiltration in the kidneys, liver, spleen and adrenal cortex (figures 1, 2, 3, 4).

*Case 2.* A 26 year old white male entered this hospital March 29, 1947, with a history of paralysis for three years. Before admission, a disarticulation of the right femur at the hip joint had been performed for chronic osteomyelitis. Nutritional state was excellent; no decubitus ulcers were present but the patient had a large urinary residual. Gynecomastia was present, however, though liver function tests were normal. On April 21, 1947, bladder neck resection was performed to reduce the urinary residual. Because of spasm of the muscles of left leg and dislocation of left hip, an arthrodesis was done on the left hip joint in June, 1947. Urinary infection occurred in October, with a calculus demonstrated in the right kidney. A right nephrolithotomy was performed October 7, 1947, and the patient did well until October 19, when a phlebothrombosis developed in the left femoral vein with a small infarction of the lower lobe of the left lung. An emergency ligation of the common femoral vein was performed. The patient continued to cough blood and on November 3, 1947, a pneumonic process in the upper lobes was noted, necessitating an oxygen tent. The pneumonia improved with antibiotic therapy. Generalized edema appeared November 5, and his condition was further complicated by a nonspecific diarrhea. The total blood proteins decreased rapidly to 5 gm. Oliguria developed and subsequently the non-protein nitrogen of the blood increased steadily to 135 mg. per cent. The patient became comatose November 9, 1947. He died on November 11, 1947, of uncontrolled kidney failure complicated by pneumonia and ileus.

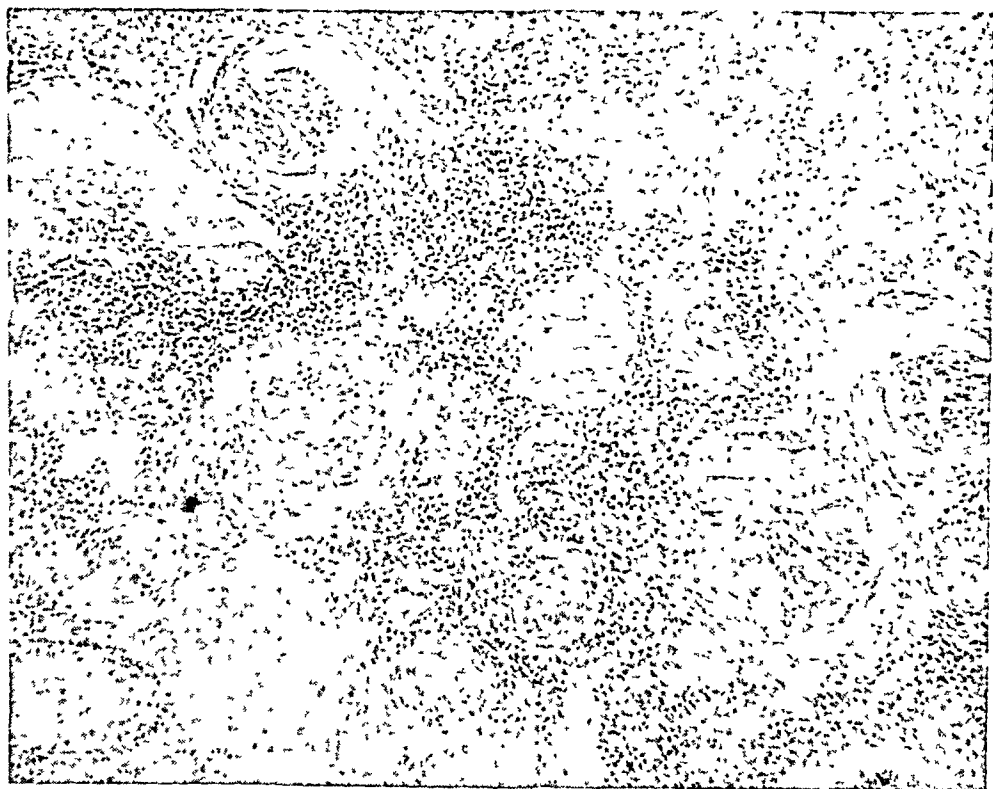


FIG. 1. *Case 1.* Renal interstitial tissue shows round cell infiltration and fibrosis. Glomeruli show varying stages of atrophy and amyloid infiltration. Amyloid degeneration is seen in proximal and convoluted tubules.

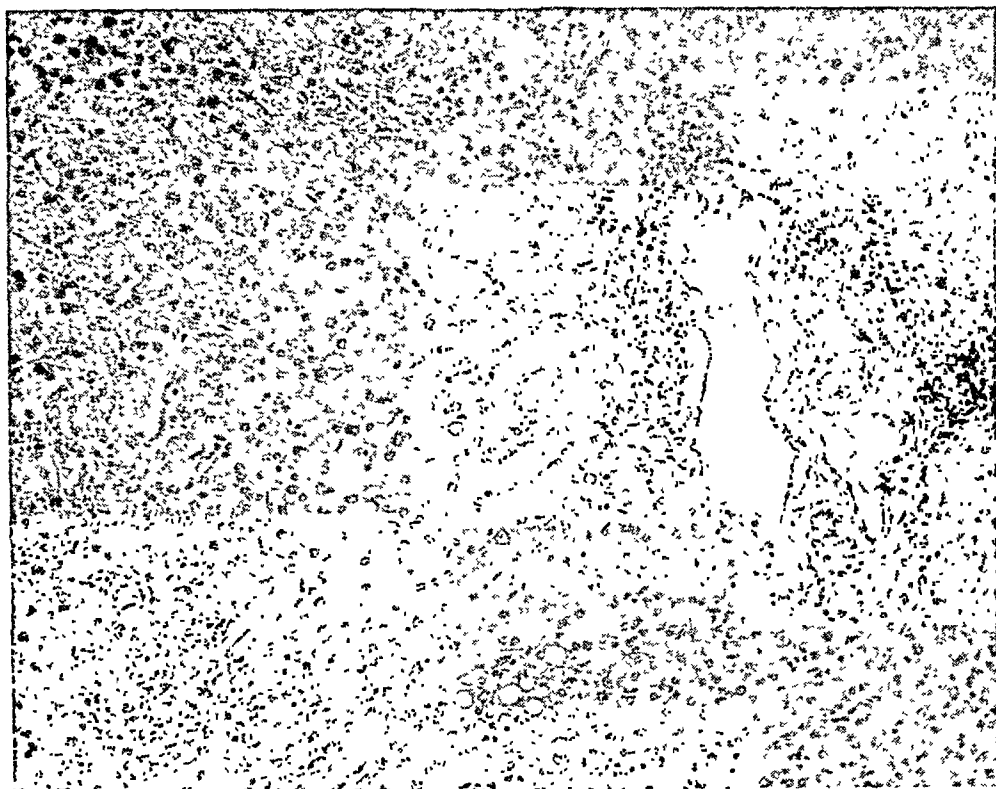


FIG. 2. *Case 1.* Liver. Showing fibrosis and round cell infiltration with pale staining amyloid material replacing the parenchymal cells.

**Pathological Findings:** Amyloid deposits in the spleen and kidneys were found at autopsy (figures 5 and 6). There was a bronchopneumonia and pulmonary infarct (left). A gastric and duodenal ulcer were also noted.

*Case 3.* In April, 1945, a 25 year old male received a gunshot wound, fracturing the fourth thoracic vertebra. A complete transverse myelopathy followed this injury. Laminectomy and suprapubic cystotomy were performed three weeks after injury. Decubitus ulcers of the ischium and trochanteric areas developed early. The ischial decubitus ulcers were closed surgically, but the ulcers in the trochanteric region at no time healed. Before admission to this hospital there was no history of renal infection or of renal calculi.

He was admitted to this hospital on January 16, 1948, as a transfer from another hospital. There were large decubitus ulcers over both trochanters, the right thigh and the sacrum. One month before admission, he suffered third degree burns of both feet. These extremities became infected following the burn, and bilateral edema was present on admission. During December, 1947, while still out of the hospital, the patient developed several loose stools which were controlled with paregoric and bismuth. Several days before his admission to this hospital he developed severe diarrhea, that was uncontrolled by previous measures. Laboratory data were negative, except for a mild hypochromic anemia and low serum protein (5 grams with A/G ratio of 1 to 1). X-ray study of kidneys, ureter, and bladder revealed no calculi.

**Course in Hospital:** Patient was placed on a low residue diet and given sulfaguanidine and paregoric to relieve diarrhea. Bacteriological examination of stools was negative throughout the illness. On January 19, 1948, three days after admission a 3 plus albumin was present in the urine. This albuminuria continued, varying between one and three plus. The severity of the diarrhea fluctuated, but was never



completely controlled. A sigmoidoscopic examination revealed a congested mucosa with petechial hemorrhages. The total serum protein had dropped to 4.3 grams by February 5. The cephalin flocculation test at the same time was 4 plus in 48 hours. Due to the similarity of these events with those of the cases presented above, the diagnosis of amyloidosis was suspected. Congo red test was performed but was negative. Attempts to improve nutrition by use of intravenous protein hydrolysate failed to elevate the serum protein or improve nutrition. Nausea, headache and oliguria appeared suddenly on March 10, 1948. Associated with this was a persistent hypotension of 80 mm. Hg systolic and 40 mm. diastolic. This was unaffected by adrenal cortical extract. Blood chemistries of March 8, 1948, showed non-protein nitrogen 40 mg. per cent, total protein 3.6 gm. with A/G ratio of .6 to 1. The non-protein nitrogen increased within a week to 132 mg. per cent and the CO<sub>2</sub> combining power decreased to 30 per cent. Hypotension increased until shock level of 30/20 was reached on March 8, 1948. Respirations became labored. Cyanosis developed and death occurred on this date.

**Pathological Findings:** The spleen, kidneys, liver and adrenals were enlarged. Amyloid deposits were noted in all of these organs, replacing most of the normal tissue.

**Case 4.** This 27 year old white male had been wounded in the chest on September 9, 1944 by a shell fragment, with accompanying fracture of the twelfth thoracic vertebra. There was immediate and complete loss of motor function and sensation below this level. A laminectomy was performed immediately and the patient transferred to the Zone of the Interior. While he was still in the Army a cordotomy was done to relieve pain. Several decubitus ulcers developed, but healed without injury. A right nephrolithotomy was performed March 12, 1946, but it was necessary to leave a large calculus. When the patient was transferred to the Veterans Administration



FIG. 3. *Case 1.* Spleen. No definite architecture is present. Stroma and malpighian corpuscles are replaced by acellular, pale staining amyloid material.

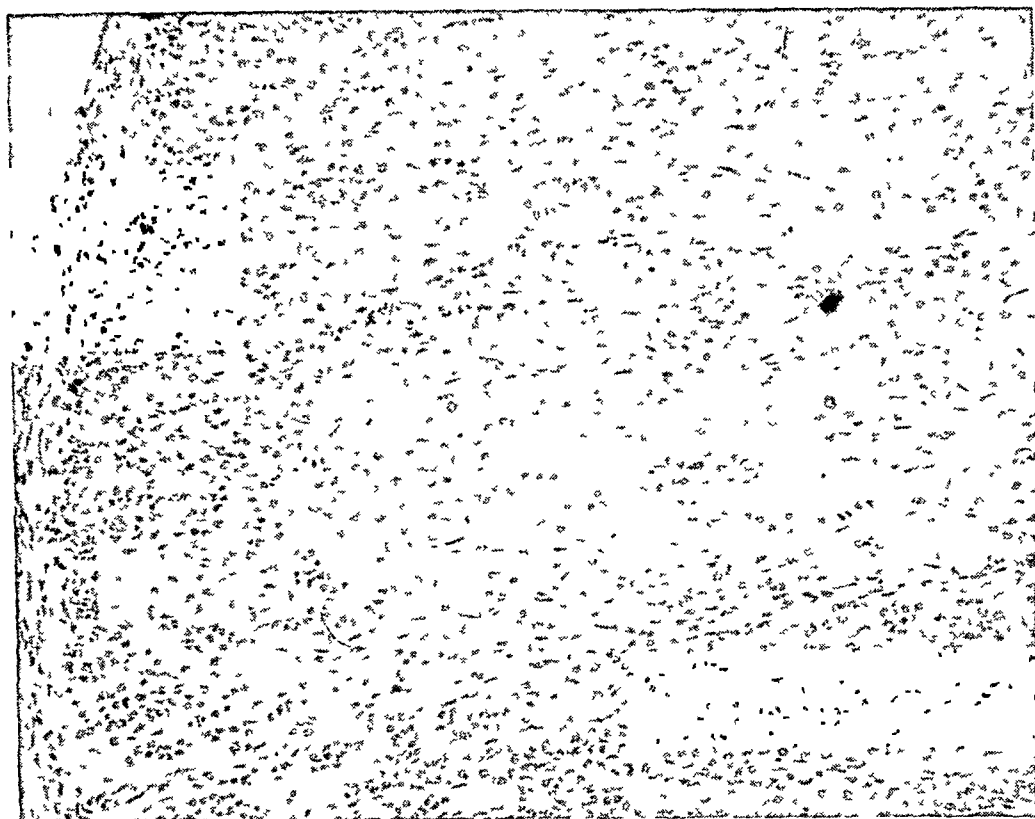


FIG. 4. *Case 1.* Adrenal cortical tissue almost completely infiltrated with amorphous, pink staining amyloid material.

on June 6, 1946, a decubitus ulcer of the right hip, a stag-horn calculus in the right kidney, and osteomyelitis of L-1 and L-2 vertebrae was present. In September 1946, the patient developed infectious hepatitis. Calculi developed in the right kidney and were removed November 8, 1946. A transurethral vesical resection was performed in March, 1947, with improvement of renal function. Several episodes of urinary infection occurred and calculi developed in both kidneys. Patient left the hospital against medical advice for six months. On September 6, 1947, he was admitted with the previous diagnoses, plus a draining sinus in the suprapubic ulcer and multiple rat bites of the lower extremities. His course following readmission steadily declined. The bilateral stag-horn calculi increased in size but the patient's general condition was too poor to consider further surgical intervention. There were repeated episodes of urinary infection and one plus to three plus albumin was always present. Liver function testing on January 15 showed bromsulfalein 20 per cent, cephalin flocculation 3 plus in 48 hours, total protein 6.5 grams and A/G ratio 1.2 to 1.

In January, 1948, amyloidosis was suspected but Congo red test was negative. Examination of the gingival tissue showed no evidence of amyloidosis. On February 3, 1948, suprapubic cystotomy was performed to increase renal function. On February 27, 1948, a spontaneous femoral thrombophlebitis, left, occurred and a bilateral femoral vein ligation was performed. The patient lost strength rapidly. Transient edema of face, genitalia and abdomen was observed the latter part of March. Total proteins at that time were 4.7 grams with .6 to 1 A/G ratio. Severe, uncontrollable diarrhea developed about one month later. Non-protein nitrogen gradually rose to 74 mg. per cent on April 4, 1948. One week before death the urine became grossly bloody. Oliguria developed and was accompanied by clinical evidence of azotemia.



FIG. 5. *Case 2.* Splenic lymphoid stroma is infiltrated with acellular, amorphous, pink staining material, characteristic of amyloidosis.

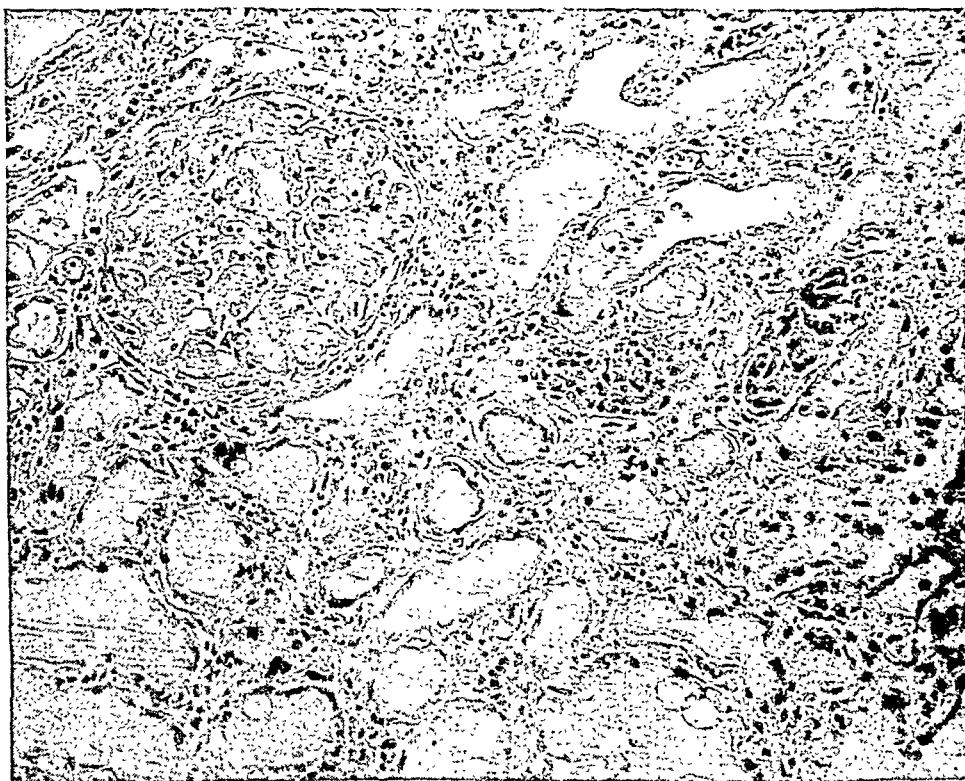


FIG. 6. *Case 2.* Renal glomeruli demonstrate marked atrophy and infiltration with amyloid material. Profuse tubular degeneration is present and it contains the pink staining material.

On May 12, 1948, respirations became labored and shallow. Constant projectile vomiting and Cheyne-Stokes respiration developed, followed by death.

**Pathological Findings:** At autopsy, amyloid deposits were noted in the kidneys and adrenal cortex. There was also periportal hepatic cirrhosis and ulcerative colitis.

### DISCUSSION

Spinal cord injury is accompanied by a triad of inflammatory processes: decubitus ulcers, chronic osteomyelitis and urinary infections. In addition to this triad there is a profound disturbance of metabolism that has not been elucidated. The fact that these patients now live long enough to be encumbered by the above processes makes amyloid degeneration a distinct possibility.

The clinical findings of secondary amyloidosis vary with the organ involved and the amount of amyloid deposited. The primary disease often masks the findings.<sup>7, 8, 9</sup> If the liver and spleen are involved, these organs usually will be palpable. Abdominal distention may accompany these findings. Purpura has been reported in several cases with splenic amyloidosis.<sup>10</sup> Jaundice, seen in Case 1, is extremely rare, having occurred only four times in the previous literature.<sup>11, 12</sup> Albuminuria obviously is a consistent sign when amyloid degeneration involves renal tissue. If albuminuria is excessive, hypoproteinemia will result. The edema of hypoproteinemia appears late in the course of the disease. Hyaline and granular casts may also appear. There is loss of the power of concentration of the kidney due to tubular damage. The severe azotemia that preceded coma and death in the cases presented is an unusual finding in amyloid disease.<sup>7</sup> When renal insufficiency and uremia occur, the process is irreversible and death is rapid as is illustrated by these cases. Adrenal involvement is a common finding.<sup>10</sup> Addison's disease as a result of amyloid deposits in the adrenal is rare; however, three of these cases presented the clinical picture of subacute adrenal cortical insufficiency.

The clinical diagnosis of amyloidosis in spinal cord injury is difficult because the findings described above are present in the ordinary complications of this injury. Malnutrition and metabolic disorders occur soon after spinal shock. Hepatomegaly is seen frequently. It has been noted in 33 of 250 patients on the Paraplegia Service here. The cause of this enlargement of the liver has not been elucidated. Cases 1 and 3 are the only patients of the 33 mentioned above in which this hepatomegaly proved to be associated with deposits of amyloid in the liver. Albuminuria is also a frequent finding resulting from urinary infection and calculi in the bladder and kidney accompanying spinal cord injury.

It is interesting to attempt to explain the cause of the non-specific bloody diarrhea in the cases presented. Two peptic ulcers were present at necropsy (Cases 2 and 4), one gastric and the other duodenal. In Case 2 there was some evidence of bleeding from the gastric ulcer. Case 4 presented ulcerative colitis. There were no amyloid deposits in the gastrointestinal tract in

any case. The mucosa of the large bowel of all cases showed congestion and hyperemia. These pathologic findings suggest that the diarrhea may have been connected with the uremic state present in these patients.

Amyloidosis associated with spinal cord injury is an unusual but not an unexpected occurrence. Since the introduction of chemotherapeutic and antibiotic agents and surgical procedures a certain measure of success has been accomplished in the treatment of the infectious complications of spinal cord injuries. This elimination of infection can be a factor in the prevention of amyloidosis. The use of whole liver as advocated by Grayzel and Jacobi<sup>13</sup> may help in the treatment of this irreversibly destructive pathological process. These combined factors should improve the prognosis of amyloid disease complicating spinal cord injury.

### SUMMARY

1. Four cases of amyloidosis proved at autopsy occurring in spinal cord injury are presented.
2. The clinical course of the patients is that of secondary amyloidosis associated with renal involvement.
3. The expected incidence of this process in spinal cord injury is illustrated by this report.

### BIBLIOGRAPHY

1. BRUNSTING, L. C., and MACDONALD, L. D.: Primary systematized amyloidosis with macroglossia; a syndrome related to Bence Jones proteinuria and myeloma, *Proc. Mayo Clin.*, 1947, xxii, 67-70.
2. HESTON, W. E., LARSEN, C. D., and DERINGER, M. K.: Variation in occurrence of pathological calcification, nephritis and amyloidosis, *Jr. Nat. Cancer Inst.*, 1945, vi, 41-47.
3. JACOBI, M., and GRAYZEL, M. A.: Amyloidosis generalized—C.P.C. 84 cases, *Jr. Mt. Sinai Hosp.*, 1945, xii, 339-363.
4. TRASOFF, A., SCHREIBER, N., and SCARF, M.: Recovery from rheumatoid arthritis complicated by amyloidosis, *Arch. Int. Med.*, 1944, lxxiv, 4-10.
5. ZEMP, E. F.: Primary amyloidosis, *Ann. Int. Med.*, 1947, xxvi, 448-453.
6. FAGGE, C.: Principles and practice of medicine, 1867 ii, 481-488.
7. AUERBACH, O., and STEMMERMAN, M. G.: Renal amyloidosis, *Arch. Int. Med.*, 1944, lxxiv, 244-253.
8. COHEN, S.: Amyloidosis complicating tuberculosis—diagnosis, treatment and prognosis, *Ann. Int. Med.*, 1943, xix, 990-1002.
9. ROSENBLATT, M. B.: Clinical manifestations of amyloidosis, *Ann. Int. Med.*, 1934, viii, 679-689.
10. EKLUND, C. M., and REIMANN, H. A.: Etiology of amyloid disease, with note on experimental renal amyloidosis, *Arch. Path.*, 1936, xxi, 1-9.
11. ORLOFF, J., and FELDER, L.: Primary systemic amyloidosis with jaundice, *Am. Jr. Med. Sci.*, 1946, ccxii, 275-279.
12. SPAIN, D., and RILEY, R.: Jaundice in amyloidosis of the liver, *Am. Jr. Clin. Path.*, 1944, xiv, 284-288.
13. GRAYZEL, H., and JACOBI, M.: Secondary amyloidosis, results of therapy with desiccated whole liver powder, *Ann. Int. Med.*, 1938, xii, 39-58.
14. AUERBACH, O., and STEMMERMAN, M. G.: Value and limitation of the Congo red test, *Am. Jr. Med. Sci.*, 1944, ccviii, 305-309.

15. TARAN, A.: Improved Congo red test, *Jr. Lab. and Clin. Med.*, 1937, xxii, 975-977.
16. TARAN, A., and ESKSTEIN, A.: Standardization of the Congo red test, *Am. Jr. Med. Sci.*, 1942, cciii, 246-253.
17. BABER, M. D.: Amyloid macroglossia, *Lancet*, London, 1947, i, 210-211.
18. BANNICK, E. G.: Diffuse amyloidosis of unknown etiology, *Med. Clin. North Am.*, 1934, xviii, 411-422.
19. BANNICK, E. G., and BERKMAN, J. M.: Diffuse amyloidosis, clinical and pathological study, *Arch. Int. Med.*, 1938, li, 978-990.
20. CORBETT, R. W., and BRODERS, A. C.: Amyloidosis of the urinary bladder, *Jr. Urol.*, 1944, lii, 153-157.
21. DICK, G. F., and LEITER, L.: Development, localization and reabsorption of amyloid in rabbits, *Am. Jr. Path.*, 1941, xvii, 741-754.
22. DIXON, H. M.: Renal amyloidosis in relation to renal insufficiency, *Am. Jr. Med. Sci.*, 1934, clxxxvii, 401-411.
23. DUNN, T. B.: Relationship of amyloidosis and renal disease in mice, *Jr. Nat. Cancer Inst.*, 1944, v, 17-28.
24. HAYMAN, J. M.: Cecil's textbook of medicine, 1942, 5 ed., 1062-1063.
25. HYMAN, A.: Association of hypernephroma with amyloidosis of the kidney, *Jr. Urol.*, 1946, lvi, 303-309.
26. JAFFE, R. H.: Influence of diet in amyloidosis, *Arch. Path.*, 1926, i, 20.
27. JAFFE, R. H.: Amyloidosis produced by injection of protein, *Arch. Path. and Lab. Med.*, 1926, i, 25.
28. KU, D. Y., and SIMON, M. A.: Influence of various diets on mice, *Arch. Path.*, 1934, xviii, 245-251.
29. KRUMBHAR, E. C.: Cecil's textbook of medicine, 1942, 5 ed., 1386.
30. KOLETSKU and STRECHER: Primary systemic amyloidosis, involvement of cardiac valves, joints and bones, with pathological fracture of femur, *Arch. Path.*, 1939, xxvii, 267-288.
31. LINDSAY, S., and KNORP, W.: Primary systemic amyloidosis, *Arch. Path.*, 1945, xxxix, 315-322.
32. MOSCHCOWITZ, E.: Clinical aspects of amyloidosis, *Ann. Int. Med.*, 1936, x, 73-88.
33. NOMLAND, R.: Localized (lichen) amyloidosis of the skin, *Arch. Dermat. and Syph.*, 1936, xxxiii, 85-98.
34. PEARSON, P., and RICE, MAURICE: Primary systemic amyloidosis; report of 2 cases in negroes with special reference to certain histological criteria for diagnosis, *Arch. Path.*, 1941, xxxii, 1-10.
35. PURCELL, H. M.: Localized amyloidosis of the urinary bladder, *U. S. Naval Med. Bull.*, 1946, xlv, 1607-1610.
36. REIMANN, H. A., and EKLUND, C. M.: Primary amyloidosis limited to tissues of mesodermal origin, *Am. Jr. Path.*, 1935, xi, 977-988.
37. ROSENBLATT, M. B.: Amyloid nephrosis, *Am. Jr. Med. Sci.*, 1933, clxxxvi, 558-567.
38. SELIKOFF, I. J.: Gingival biopsy for diagnosis of generalized amyloidosis, *Quart. Bull. Sea View Hosp.*, N. Y., 1946, viii, 4.
39. SOLOMON, W.: Amyloidosis in chronic atrophic arthritis, *Ann. Int. Med.*, 1943, xviii, 846-850.

# THE DIAGNOSIS OF PNEUMONIA PRECEDING TUBERCULOSIS \*

By ALVIN S. HARTZ, M.D., *Baltimore, Maryland*

A LARGE proportion of the patients admitted to the Tuberculosis Division of the Baltimore City Hospitals for the first time had previously been acutely ill with what was diagnosed as pneumonia. The acute illness occurred at a period when it might be assumed that a tuberculous process was present. In most instances the disease was in a far advanced stage when the diagnosis of tuberculosis was made subsequent to the acute illness. In some cases, death occurred from tuberculosis soon after acute symptoms suggesting pneumonia, and diagnosed as such, developed. Many more individuals gave histories of influenza and grippe a relatively short time before the diagnosis of tuberculous infection was established.

An attempt has been made to analyze those cases of tuberculosis with acute symptoms, excluding those called influenza and grippe, and including only those with the most severe picture namely those which a physician had called pneumonia. Five hundred charts were selected at random from the files of the City Hospitals Tuberculosis Division and the records of those patients with a history of pneumonia selected for further study. When the patient had been treated at home by a private physician, the history as given by the patient had to be relied on completely. When patients had been hospitalized and the diagnosis of pneumonia made, either the old chart or an abstract of the record was obtained, if possible.

It was found that of the 500 patients, 71 or 14.2 per cent gave a history of pneumonia with a time relationship such that it was possible or likely that the illness was related to the tuberculous infection in some way. Many more gave a history of an acute illness called influenza, but these were not investigated further. Of the 71 patients, 48 had been treated for pneumonia at home and 23 had been cared for in a hospital. The age, sex, and racial distribution were similar to those of the Tuberculosis Division except for the small number of Negro women in the group, nine in all. This estimate of the proportion of patients with tuberculosis, who had been diagnosed as pneumonia, does not include those instances in which the symptoms of the acute illness or the clinical course of the disease had suggested tuberculosis and in which further studies had then established the diagnosis of that disease during the hospital stay. Thus, in almost 15 per cent, it was judged that some harm had been done by diagnostic failure either to the patient or his contacts.

There are three explanations of why pneumonia had been diagnosed: (1)

\* Received for publication December 13, 1947.

From the Division of Tuberculosis, Baltimore City Hospitals.

TABLE I  
Showing Clinical Data on Patients Discharged from General Hospital with Pneumonia Preceding Tuberculosis  
(Only those included, on whom adequate information available)

Name	Sex	Age	X-Ray Reading Gen. Hospital	WBC— Gen. Hosp.	Temperature	Elapsed Interval	X-Ray TBC Hosp.
1. H. W.	WF	39	Mottled fibrous densities in left first interspace. Densities in lower left chest and hilum. No essential changes, later. Considered atypical pneumonia.	8,400	104°(R) on admission. On penicillin and sulfadiazine, drop to normal in five days but persistent low grade fever to 99.6° on discharge.	11 mos.	Diffuse infiltration involving entire left lung, also infiltration at right base. Positive sputum.
2. E. B.	CM	47	Mottled shadows, density over entire left lung and lower portion of right. Marked clearing hilar region later.	18,800–12,000 11,000–14,000	104 to 105° on admission—gradually subsiding but never disappearing completely. No chemotherapy.	5 mos.	Right lung clear. On left—infiltration from apex to fourth rib with mottling to base.
3. J. H.	CM	47	Large area of consolidation base of right lung with fibroid infiltration left apex. Discharged, diagnosis—acute lobar pneumonia RLL type undetermined with delayed resolution.	32,400	Temperature fell by crisis. No chemotherapy.	Approx. 3 yrs.	1st admission for TBC, x-ray reading not available.
4. J. M.	CM	48	Consolidation right upper lobe.	2,500–17,400	104 to 101° to low grade fever after one week. Sulfonamides.	3 mos.	Infiltration right upper lobe.
5. J. F.	WM	71	Pneumonic density, left upper lobe.	8,200–9,000	100–104° for nine days, went down to 99.4°.	2 mos.	Bilateral apical disease minimal.
6. E. R.	WM	50	Consolidation upper 2/3 right lung, no change until two months later when slight clearing was reported.	5–8,000	From 105° to normal in five days. Low grade thereafter.	1 year	Far advanced disease right upper lobe with cavity.



TABLE I—Continued

Name	Sex	Age	X-Ray Reading Gen. Hospital	WBC— Gen. Hosp.	Temperature	Elapsed Interval	X-Ray TBC Hosp.
7. J. C.	CM	23	Minimal infiltration infraclavicular area. Râles heard over LLL considered to be site of pneumonia.	5-11,000	105° on admission. Rapid fall to 99° with sulfonamide.	5 years	Far advanced bilateral.
8. J. K.	WM	57	Clouding in left mid-lung, patchy infiltration in left base and old fibrous infiltration in right upper lung.	18,600	Temperature persisted. Empyema blamed. Positive blood culture for pneumococcus not typed.	1 year	Location—upper $\frac{2}{3}$ both lungs, positive sputum. Died in 13 days.
9. T. R.	CM	43	Dense clouding through greater portion of upper right lung.	24,500	Down to normal in one day; after seven days up to 99 to 100°. Recurrence. Temperature again to normal. Received sulfonamides.	9 months for diagnosis.	Right upper lobe moderately advanced.
10. G. M.	WM	55	Consolidation LUL, some clearing on serial films.	16,500 with 89% polys.	Nineteen days for temperature to return to normal.	2½ years	Left upper lobe.
11. A. B.	WM	55	Patches of bronchopneumonia. Each lower lung.	7,300	100 to 102° for eight days; then 99 to 100° subsiding in one week.	38 mos.	Consolidation upper half left, patchy right mid-lung.
12. S. M.	CF	30	Infiltration left and right apex and right base probably due to resolving pneumonia. No change before discharge.	28,850	103° on admission to normal in three days. Secondary elevation. Received sulfonamides.	15 mos.	Throughout both lungs bilaterally.
13. T. M.	WM	65	Density over entire left lung field which showed some clearing.	19,000 down to 10,500	100 to 101°, gradually fell to 99 to 100° on discharge with penicillin.	7 mos.	Bilateral extensive.

The patient had pneumonia without tuberculosis. The illness may or may not have contributed to the later development of tuberculosis. (2) There was a pneumonia superimposed on a tuberculous infection. (3) The findings were misinterpreted as being due to pneumonia when actually due to tuberculosis. It is probable that the largest number of cases fall in the last group, of which the following case histories are illustrative:

A 38 year old white man was admitted with tuberculosis on June 27, 1945. He had complained of malaise and fatigability for two years but of no other significant symptoms. In the late winter of 1944, he developed a cold with a fever and cough.



FIG. 1a. Consolidation right upper lobe. Diagnosis: pneumonia.

This was diagnosed as bronchopneumonia and after treatment with sulfonamide and bed rest at home, he felt fairly well. In March 1945, there was another acute episode and again the symptoms subsided on rest and chemotherapy. In May 1945, the symptoms recurred. A roentgenogram showed far advanced tuberculosis.

A 50 year old white man was first admitted to Baltimore City Hospital on March 18, 1942. His temperature was 105° F. and a roentgenogram showed consolidation of the upper two-thirds of the right lung. His temperature subsided within five days

while he was on sulfonamide therapy. The leukocyte count ranged between 5,000 and 8,000. One month after admission, there was only slight clearing of the consolidated area. Sputum studies yielded a type 5 pneumococcus. One year later he was admitted with a positive sputum and a diseased right upper lobe.

A 48 year old Negro male was admitted to a general hospital in November of 1943. On admission there was consolidation of the right upper lobe. The temperature was 104° and fell to 101° within a week. The leukocyte count was 2,500 on ad-



FIG. 1b. One year later. Disease right upper lobe. No acute symptoms, sputum positive for tubercle bacillae.

mission but rose to 17,400 after four days. Type 12 pneumococcus was obtained from the sputum by mouse inoculation. The discharge diagnosis was unresolved pneumonia. In May of 1944, he was admitted to City Hospitals with positive sputum and disease of the right upper lobe.

Several instances were encountered where non-tuberculous pneumonia had in all probability accompanied a pulmonary tuberculosis:

A 29 year old Negro male was admitted to a general hospital in September of 1942 with the complaint of severe pain in the left chest of 12 hours' duration. The

temperature was 100° rectally with a leukocyte count of 20,400. Physical and roentgenologic signs indicated lobar infiltration at the right base. In spite of physical signs at the right apex there was no roentgenologic evidence of disease in that area. No pneumococci were found in the sputum but on two occasions acid fast organisms were found. He was transferred to the City Hospitals, where the positive sputum was confirmed. The consolidation at the right base cleared; a minimal degree of infiltration at the right apex remained. He signed out after a few months of hospital care. In 1946, he was re-admitted in a critical condition with far advanced disease.



FIG. 2a. Acute onset of illness, consolidation of left upper lobe. Five weeks later: some resolution of process. Sputum negative for acid fast organisms.

A white man of 55 was first admitted to the City Hospitals in March of 1944. The temperature was 103°, the leukocyte count 16,500 with 89 per cent polymorphonuclears. The roentgenogram showed consolidation of the left upper lobe. The temperature returned to normal slowly while the patient was under treatment with sulfadiazine. Five sputum examinations were negative for acid fast organisms. No pneumococci were detected. In October 1946, he was admitted again with an almost identical story. The temperature was 105° and the white count 23,000. He was severely dyspneic. The temperature and white count returned to normal after 24 hours as did his respiration, during the administration of penicillin. The sputa were

positive for tuberculosis. The roentgen-ray of the chest was virtually identical with that obtained in 1944. It showed dense infiltration in the left upper lobe and perihilar density on the right which rapidly cleared.

There are a number of factors which account for the difficulty in distinguishing clinically between acute non-tuberculous pneumonia and pulmonary tuberculosis:

(a) The first definite clinical symptoms of tuberculosis may consist of an episode of high fever which subsides in a few days. Such cases are not always advanced in extent.

In a hospital worker with the complaint of chest pain and sudden onset of fever of 102°, a roentgenogram showed a minimal tuberculous lesion. The symptoms and fever disappeared in 24 hours. Now, five years later the patient has far-advanced pulmonary tuberculosis.

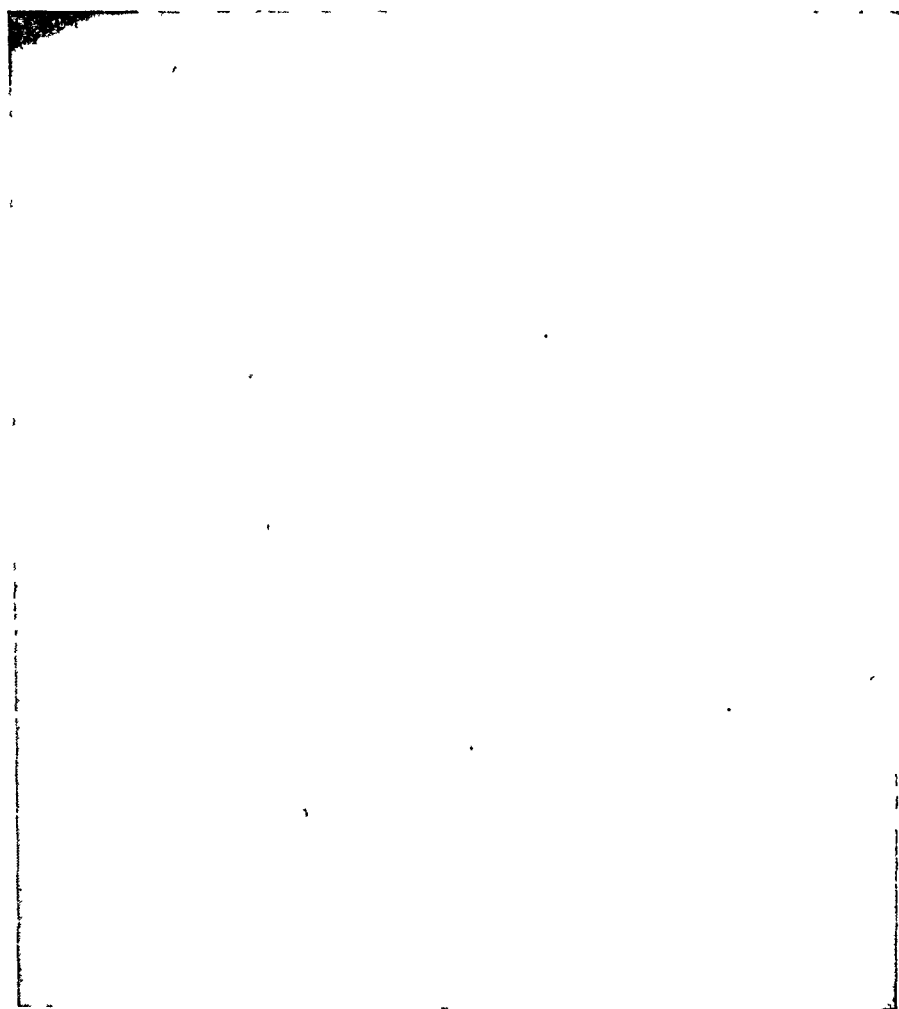


FIG. 2b. Readmission film 19 months later. Fever, dyspnea responding promptly to penicillin, positive sputum. Infiltration above right diaphragm completely resolved.

(b) The white count may be elevated in tuberculosis to as high levels as in lobar pneumonia.<sup>2</sup> It has been stated that one-fourth of the patients with far-advanced disease have white counts between 12,000 and 18,000, on admission.

(c) The fact that the tuberculous process may be restricted to a lower lobe may suggest a non-tuberculous pneumonia.<sup>3</sup>

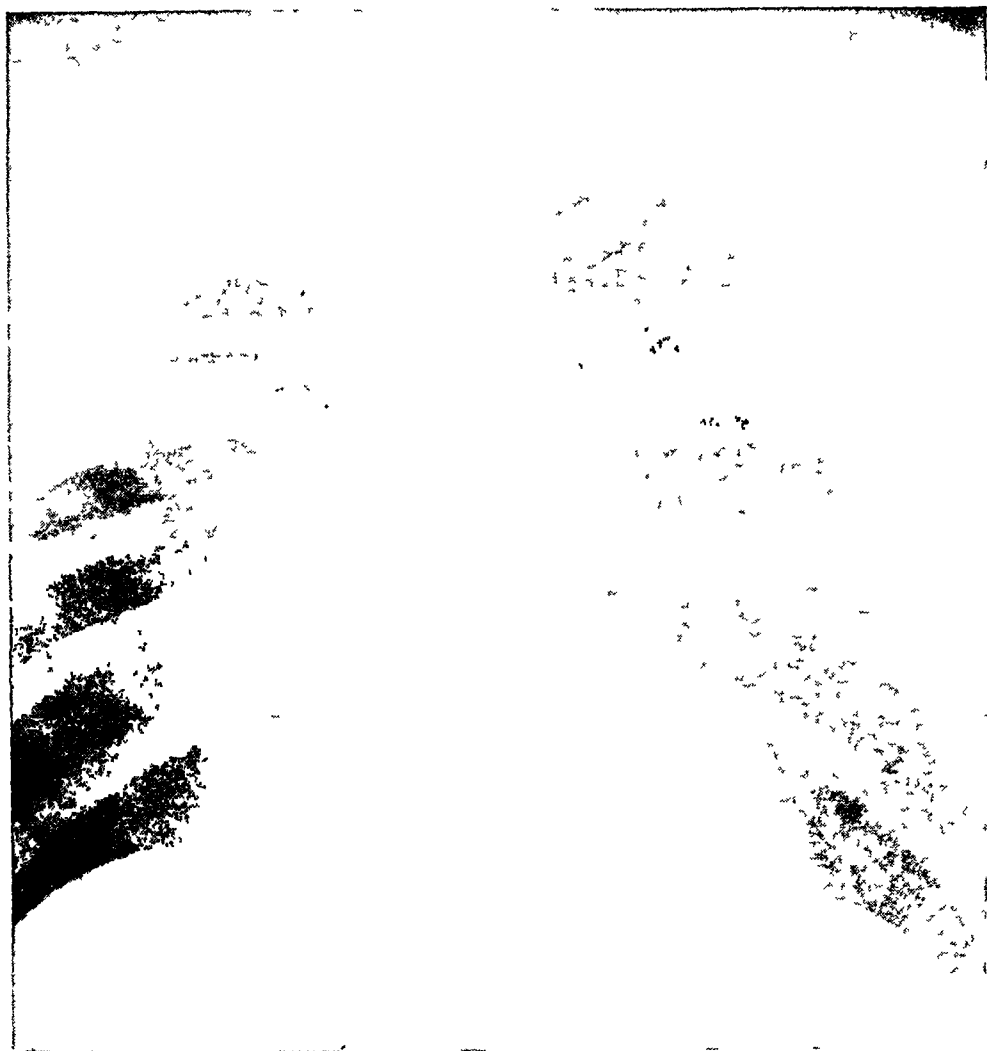


FIG. 3a. Film taken on outpatient basis. No acute symptoms, no sputum obtained. Diagnosis of tuberculosis made because of film.

(d) In early tuberculosis prior to caseation there may be great difficulty in obtaining a positive sputum.

(e) Even the course of the disease, which is usually decisive, may at times prove misleading. While in general non-tuberculous pneumonias resolve in a few weeks and tuberculous infiltrations persist, there are exceptions to both of these rules. Primary atypical pneumonia has been known to give roentgenographic changes for three months.<sup>6</sup> On the other hand, exudative, tuberculous lesions may disappear within the same length of time.

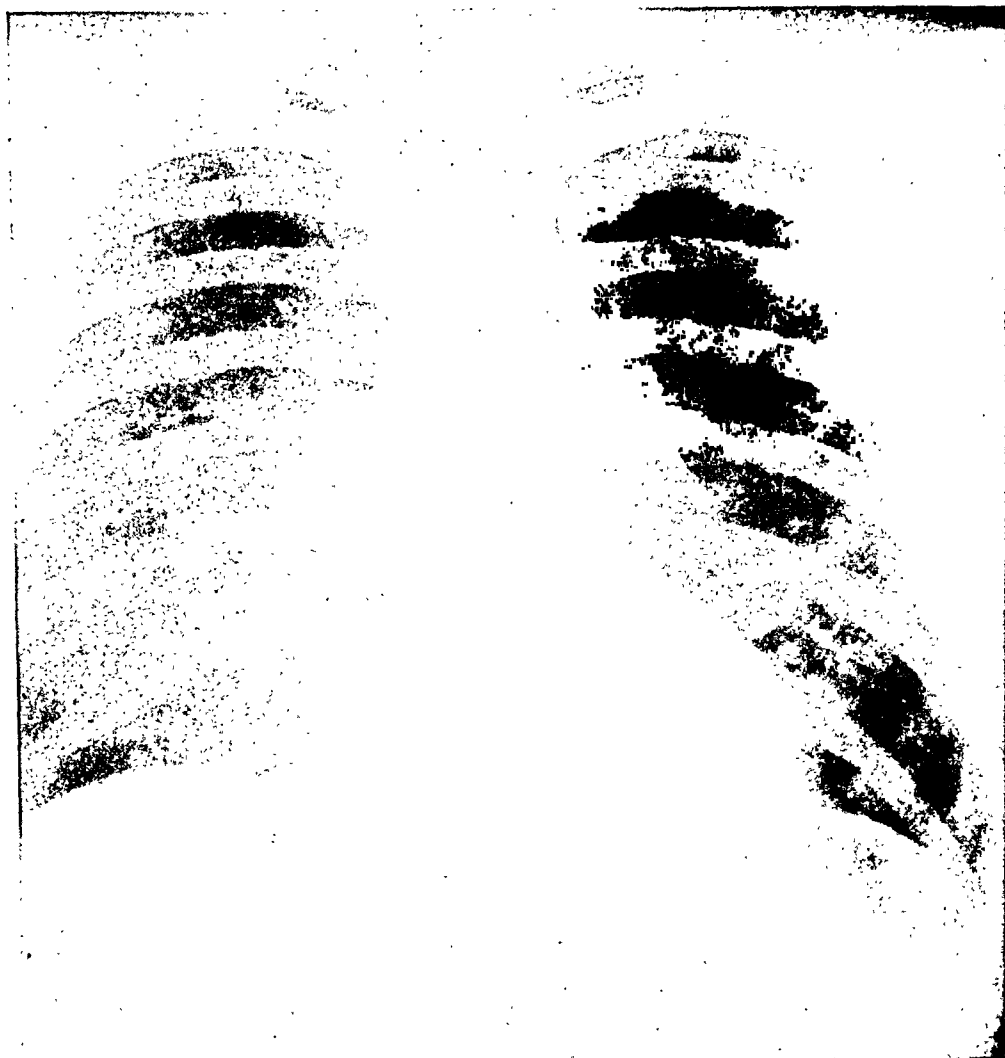


FIG. 3b. Admission to tuberculosis hospital in four months. Negative chest, discharged to mental institution.

A white male alcoholic was admitted in April, 1943 because a roentgenogram taken in December, 1942 had shown infiltration throughout the right upper lobe. On admission in April, however, his film was negative, and he was discharged to a mental institution because of delirium tremens a few days after admission. One year later he was readmitted with a far-advanced tuberculous process throughout both lungs and a positive sputum.

In this case unequivocal proof that the original lesion was tuberculous is, of course, lacking, but there have been reported instances similar to this where the initial diagnosis of tuberculosis was more positive. Ornstein, Ulmar and Dittler<sup>5</sup> have described a picture of benign, exudative tuberculosis where the exudative lesion disappears entirely. They collected 58 cases, most of them with positive sputum, in whom all roentgenographic evidence of tuberculosis cleared within six weeks to several months. Amberson<sup>4</sup> in

discussing the process of resolution states that it proceeds slowly and stops at the barriers of unresolvable, caseous centers. It is certainly conceivable that, if there is minimal caseation, resolution may be complete enough so that the residual caseous center may be invisible on the roentgenogram.

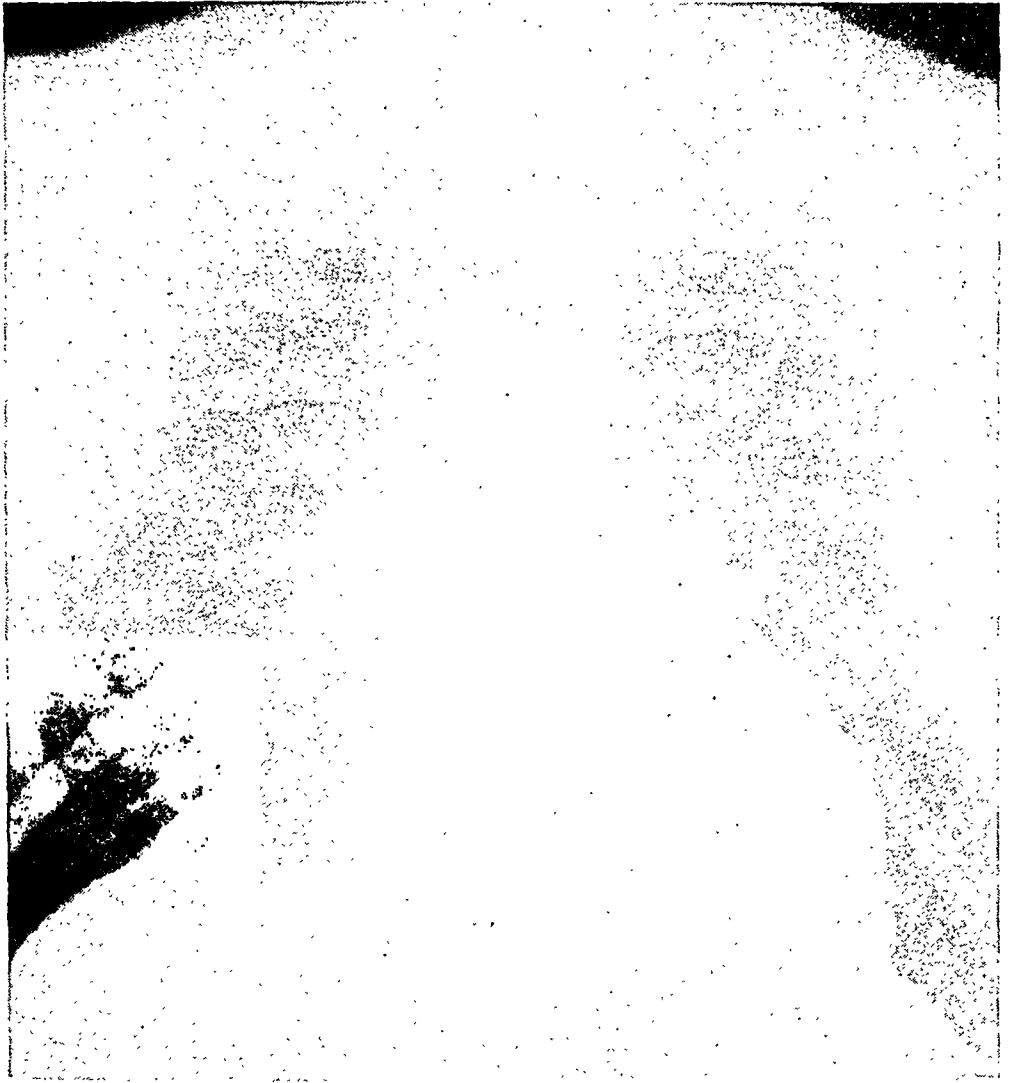


FIG. 3c. Readmission to tuberculosis division 15 months later. Positive sputum.

In view of these facts, it is not difficult to understand why difficulties in diagnosis may arise as between a non-tuberculous pneumonia and pulmonary tuberculosis.

#### DISCUSSION

Very little is found in our literature concerning an antecedent history of pneumonia in tuberculosis. Flick<sup>7</sup> is quoted as stating that one-fifth of all tuberculous patients gave previous histories of pneumonia. Baum and Amberson<sup>8</sup> consider the possibility that these and other reported instances



of patients with pneumonia prior to tuberculosis were initially, in fact, tuberculous. An acute onset of tuberculosis, according to Pinner<sup>9</sup> occurs in about one-half the cases. Farber and Clarke<sup>10</sup> have reported 100 cases admitted to a general hospital for non-tuberculous causes, who were found to be tuberculous. None of these cases was admitted with the diagnosis of pneumonia. In an emphatic and eloquent address, Rist<sup>11</sup> pointed to the strong possibility of a diagnosis of lobar pneumonia being made in tuberculosis. In almost 50 per cent of 300 consecutive admissions there was an acute onset of which the following description is given:

. . . "it has the appearance of an acute pulmonary or pleuropulmonary episode. Chills and fever initiate it, the fever being generally high. Pain in the sides, coughing, expectoration are always present. The sputum may be rusty as in ordinary lobar pneumonia; dullness or flatness, tubular breathing, and crepitant râles. But it is a kind of pneumonia which either aborts after two, three or four days or on the contrary, drags on much longer than the classical nine days, becoming meanwhile, more or less atypical". . . . "The first stage with its sudden onset may be followed almost immediately by the classical symptoms of manifest phthisis. But it is generally not so. In most instances what takes place after the acute onset is a phase of quiescence or semi quiescence which has the unfortunate effect of appeasing the anxieties of both the patient and physician. Fever has subsided. Appetite comes back. One speaks of convalescence and recovery."

It is difficult to reconcile the occurrence of pneumonia in 14.2 per cent of our 500 cases during the time tuberculosis might have been suspected and the almost unanimous opinion of the unusual concurrence of pneumonia and tuberculosis. The idea that the two together constitute a rarity is so widespread that an article has appeared relatively recently describing two such cases.<sup>12</sup> Hogan<sup>13</sup> reviewed 111 cases with the combined diagnosis of pneumonia and tuberculosis occurring between 1936 and 1944 and found the incidence of tuberculosis among those with pneumonia to be 1.6 per cent. Of the 111, however, 43 were pneumonias of undetermined etiology and more than 50 per cent of the total ran an atypical course. He concludes that the incidence of pneumonia complicating tuberculosis is significantly low and that there was activation of tuberculosis in 15 per cent of his cases. Baum and Amberson do not consider the coexistence of the two processes to be quite as rare as had been supposed. Activation of the tuberculosis was seen to occur when there was an associated suppurative process in the region of the tuberculous disease.

It thus appears that the number of our tuberculous patients giving a history of pneumonia is far greater than would be anticipated from information in the literature. This may be due to our getting the history from the charts of patients in a tuberculosis hospital rather than relying on the discharge diagnosis from a general hospital, as well as the inclusion of the large group of patients who were treated at home for pneumonia. There is evidence that a significant proportion of our 71 patients had an acute tuberculous onset rather than pneumonia. If such mistakes in diagnosis were made in a hos-

pital, it is evident that the possibility of this costly mistake in diagnosis is increased when the patient is treated at home. In recent years with the advent of chemotherapy, and antibiotics, home treatment of acute respiratory disease is more common. There is a tendency to class resistant cases as primary atypical pneumonia. It cannot be too strongly emphasized that the possibility of tuberculosis as the etiologic factor should be kept in mind in all acute pulmonary disease. Sputum examinations and follow-up chest films are of great importance if error is to be avoided.

### SUMMARY

Of 500 unselected cases of tuberculosis, 14.2 per cent gave a history of acute illness diagnosed as pneumonia within the period in which tuberculosis might have been expected to be present. This incidence is far greater than would be expected from the reported coincidence of pneumonia and tuberculosis. The findings in an acute tuberculosis may simulate those of pneumonia. There is evidence that in certain of these tuberculous patients, the symptoms resulting in a diagnosis of pneumonia were, in fact, due to tuberculosis.

### BIBLIOGRAPHY

1. KINGHORN, H. M.: The diagnosis of tuberculosis, *Jr. Am. Med. Assoc.*, 1940, cxv, 1614-1620.
2. STOBIE, W., ENGLAND, N. A., and McMENEMY, W. H.: Interpretation of the hemogram in tuberculosis, *Am. Rev. Tuberc.*, 1942, xlv, 1-26.
3. SOKOLOFF, M. J.: Lower lobe tuberculosis, *Radiology*, 1940, xxxiv, 589-594.
4. AMBERSON, J. B., JR.: The process of resolution in pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1936, xxxiii, 269-301.
5. ORNSTEIN, G. G., ULMAR, D., and DITTLER, E. L.: Benign acute pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1931, xxiii, 223-247.
6. GOODRICH, B. E., and BRADFORD, H. A.: Recognition of virus type pneumonia, *Am. Jr. Med. Sci.*, 1942, cciv, 163-179.
7. FLICK, K. F.: Third Annual Report (1905-1906), Henry Phipps Institute, Philadelphia (quoted by Baum and Amberson).
8. BAUM, O. S., and AMBERSON, J. B., JR.: Non-tuberculous pulmonary infections complicating pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1943, xlv, 243-279.
9. PINNER, M.: Pulmonary tuberculosis in the adult, 1945, Charles C. Thomas, Springfield, p. 270.
10. FARBER, J. E., and CLARKE, W. T.: Unrecognized tuberculosis in a general hospital, *Am. Rev. Tuberc.*, 1943, xlvii, 129-134.
11. RIST, E.: The sudden onset of lung tuberculosis and its lobar localization, *Canadian Med. Assoc. Jr.*, 1929, xxi, 143-152.
12. PEDIGO, G. W., JR., and COLEMAN, E. O.: Pneumococcal pneumonia complicating pulmonary tuberculosis, *Am. Rev. Tuberc.*, 1941, xliii, 258-262.
13. HOGAN, G. F.: Non-tuberculous pneumonia complicating pulmonary tuberculosis, *New England Jr. Med.*, 1945, ccxxxiii, 547-556.

# CLINICAL OBSERVATIONS ON ATYPICAL LICHEN PLANUS AND RELATED DERMATOSES PRESUMABLY DUE TO ATABRINE TOXICITY \*

By AARON FEDER, M.D., *Jackson Heights, N. Y.*

ATYPICAL lichen planus is a new clinical entity borne of the tropical phase of World War II. One of the notable events in the military medical history of the Southwest Pacific was the widespread disability of troops because of dermatological disease. Most of the dermatological casualties consisted of those suffering from what was ultimately called atypical lichen planus, from eczematoid dermatitis and from a severe form of exfoliative dermatitis. During the course of the New Guinea campaign, medical officers became aware of a disease of rapidly increasing incidence which bore a striking, though superficial, resemblance to lichen planus, but which was occurring so widely and was so progressive in nature that it soon became obvious that this disease was a new clinical entity. Schmitt and Nisbet are reported<sup>1</sup> to be the first to have called attention to the disease and to have suggested its probable etiology. For want of a better name, and because of its striking similarity to temperate climate lichen planus, it was referred to as atypical lichen planus and by this name it soon became officially identified in the medical nomenclature of the service. As more was learned about this disease it was felt by some that the choice of the name was an unfortunate one, because the disease itself is distinct from the ordinary lichen planus, and because there was much to suggest that it was merely a cutaneous manifestation of a generalized morbid state. Furthermore, unlike lichen planus, there was much to suggest the true etiology of this disease.

In addition to atypical lichen planus two other important dermatological conditions were of related interest. One of these was a bizarre eczematoid dermatitis usually severely exudative. This eruption featured a marked bilateral symmetry almost mirror-like in character. Finally, there were many patients suffering from exfoliative dermatitis wherein no apparent etiology could be demonstrated. This type of exfoliative dermatitis occurred frequently. It was severe; it presented secondary weeping, crusting, and infection, and was sometimes fatal.

We observed patients with atypical lichen planus who had the eczematoid dermatitis associated with it. Patients with atypical lichen planus not infrequently progressed into a state of universal exfoliative dermatitis. On the other hand, many patients with either the exfoliative dermatitis or the less severe symmetrical eczematoid dermatitis often, while under observation, developed lesions which we regarded as characteristic of atypical lichen planus. We felt that it was necessary to identify this characteristic lesion

\* Received for publication March 18, 1948.

before a diagnosis of atypical lichen planus could be made. During 1944 and early in 1945, many who were interested in the clinical study of these diseases felt that enough clinical evidence existed to ascribe a common etiological denominator to all three of these conditions.

### CLINICAL MANIFESTATIONS

*Age:* In one of our series of 21 unselected cases of atypical lichen planus in enlisted men who were being observed at one time in a ward of an Army General Hospital in New Guinea, the range of ages was from 24 to 46. The average age for the group was 31. This was older than the average age of the enlisted personnel suffering from other diseases in the hospital. The early impression that the disease was more common and more severe in the older age group seemed to be consistently borne out as greater experience with this disease was had.

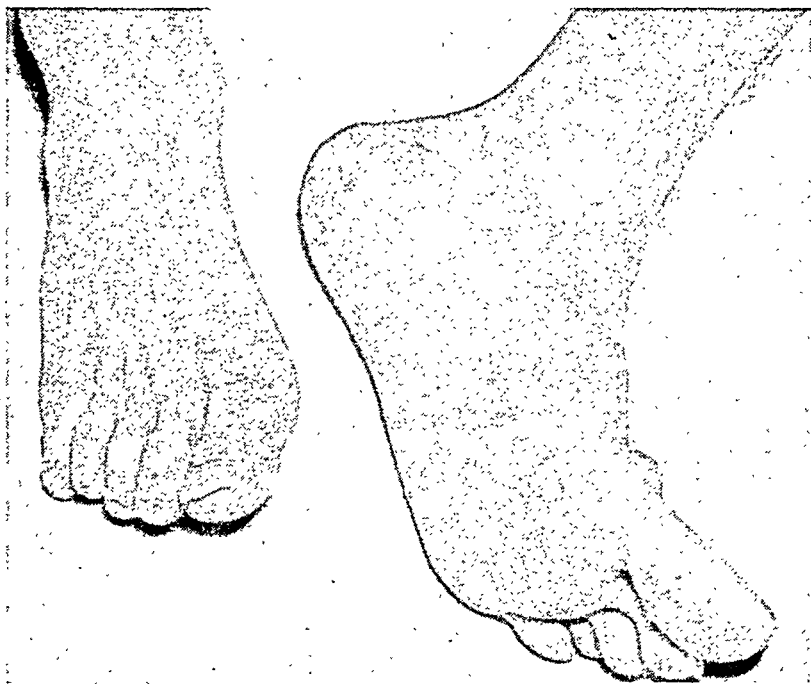


FIG. 1. Case A. B., showing extremely hypertrophic lesions.

*Time of Onset:* In the same group of 21 patients, a striking similarity in the time of occurrence of the disease was apparent. No patient in our series developed his disease prior to his being in New Guinea or, as later became evident, in the Philippine Islands, for two months. With one exception, each of the 21 patients observed his initial lesion two to five months after his arrival in New Guinea. One of the 21 did not develop his eruption until nine months had elapsed. This inclination for the disease to occur during this interval of time became an important diagnostic factor as it became apparent that the disease manifested itself neither within the first

few weeks nor after the soldier had been in the area for a long time. Thus, the appearance of a skin lesion in the second year of the soldier's tour in the area argued against a diagnosis of atypical lichen planus.

We observed, however, that many of our patients with atypical lichen planus had been in the overseas theater for long periods of time before coming to New Guinea. Although many of these had had tours of duty of varying duration in Australia, the onset of disease seemed to be related to their arrival in New Guinea. Later on in our study we observed many cases in a division which had seen service in the Hawaiian Islands for over a year prior to their being sent to New Guinea. The onset of atypical lichen planus among some of them occurred two to six months from the time they first arrived in New Guinea and, since they soon travelled on from New Guinea to the Philippine Islands, many other cases first became apparent shortly after they arrived in the Philippines. Troops who had been in other areas of the Pacific, where malaria is not endemic, before coming to the Southwest Pacific or to the Philippine Islands, presented their first cases of atypical lichen planus after their arrival in the latter areas.

*Geographic Distribution:* During the New Guinea phase of the war, it was suggested by some that atypical lichen planus was a disease limited to a particular area of New Guinea itself. Later on, when it was evident that the troops stationed throughout New Guinea added to our series of case-studies it was suggested that perhaps New Guinea alone was the home of this disease. Careful investigation into the location of individuals when the disease appeared, or before it appeared, soon dissipated that impression and the additional suggestion that the disease might have been related to sensitivity to vegetation peculiar to that area. Investigation into the backgrounds of our patients demonstrated that the disease occurred anywhere in New Guinea or the adjoining islands where there were known aggregations of troops. Furthermore, instances of the disease appearing in other theaters of operations, including the China-Burma-India theater and Italy,<sup>1,2</sup> indicated a more widespread distribution of the disease than had been supposed. The author not only observed patients in the Southwest Pacific but, after the war, when stationed in a General Hospital in the United States, had occasion to see instances of the disease in personnel returned from Burma. The clinical characteristics of the disease in those patients returned from Burma were identical to those observed in his own series of several hundreds in New Guinea and the Philippines.

During the early part of the Philippine campaign there seemed to be a sudden decrease in the number of patients. The expectation that we might find a disappearance of the disease was soon abandoned when as many cases as we had seen in New Guinea seemed to be appearing in troops who had never been in New Guinea. It was apparent then that it was just a question of the newly arrived personnel having to live through the first two or three months before cases of atypical lichen planus appeared among them. The disease among these troops who had never been in New Guinea was identical

to that seen the year before in New Guinea and in so far as we were able to ascertain, this disease had never been described as an affliction of Americans or Filipinos living in the Philippine Islands before the war.

*Sex:* The disease occurred among male and female personnel with equal severity. The relative incidence in each could not be determined.

*Race:* Atypical lichen planus was more common in soldiers of the Caucasian race. Few cases appeared among Negro troops, but they had some. One of our very sick patients was an American soldier of Japanese descent.



FIG. 2. Case C. D., discrete and confluent hypertrophic lesions in a Chinese-American soldier.

Another one of our patients was an American of Chinese origin. One very sick patient, an elderly Filipino Scout, developed his disease not during Japanese occupation but rather afterwards when he was recalled to service.

*Description of Lesion:* The characteristic lesion of atypical lichen planus is a well defined, flat-topped, hypertrophic papule, the border of which is irregular and angular. It has a violaceous hue of varying intensity so that some lesions are almost a deep slate blue color. The surface has fine scales and is striated. At first the lesions are discrete but later they tend to

coalesce. When coalescence occurs, the entire skin in the area takes on a markedly lichenified appearance. Other secondary changes occur in the surrounding skin. Outstanding among these is a follicular hyperkeratosis. This is most prominently seen over the upper back and forehead, and associated with it there is often a noteworthy absence of sweating. One-third of the 21 cases previously mentioned had associated eczematoid lesions. Three of those 21 cases had lesions in the scalp, and when scalp lesions occurred alopecia areata co-existed almost invariably. A large number of patients presented an unusual type of fine generalized scaling of the skin which appeared in lace-work pattern. This was particularly striking on the abdomen, chest and back. The earliest lesions seemed to favor the exposed areas of the body, the upper eyelids and the dorsum of the hands being most often involved. Later extension of the disease occurred along the flexor surfaces of the arms and forearms and along the inner aspect of the thighs and upon the dorsum of the feet. The genitalia and perineum were frequently involved, and occasionally the only demonstrable lesions present were on the penis. About one-third of our cases presented oral lesions usually in the form of irregular, non-ulcerated, grayish white patches on the buccal mucosa. Less frequently similar lesions were found on the palate and tongue. Stellate linear fissures in the perianal skin were a characteristic finding. Goldberg<sup>3</sup> reported findings similar to those in the mouth occurring in the anal mucosa in many patients in whom proctoscopic examination was performed.

Occasionally dark grayish-blue pigmentation of soft and hard palate and the nails also occurred concomitantly. This latter finding was likewise found at times in patients not suffering from any cutaneous disease and was attributed to pigmentary changes incident to the taking of atabrine for long periods of time.

No jaundice, hepatomegaly or nervous system involvement were observed. Splenomegaly and lymphadenopathy did not occur in patients in whom significant secondary infection was absent.

*Laboratory Findings:* In the uncomplicated non-exudative cases there were no regularly observed changes in the leukocyte count, sedimentation rate, urinalysis, blood protein, or A/G ratio determinations. Dantzig and Marshall<sup>4</sup> reported normal liver function tests in a group of patients studied by them. Epstein<sup>5</sup> reported low blood protein and calcium and high blood phosphorus values in his group of 65 patients. He also reported no regularly occurring eosinophilia. Whereas we, too, did not find eosinophilia in the uncomplicated cases, it was a frequent finding in those with the exfoliative dermatitis. Rosenthal<sup>2</sup> on the other hand, reported frequent eosinophilia in atypical lichen planus.

Many of our patients had moderate normochromic and hypochromic anemia. We observed no true aplastic anemia or severe granulocytopenia, though these are known to have occurred. One of our patients with a very severe hypoplastic anemia required multiple transfusions. Most and Hay-

man<sup>6</sup> reported a study on the blood findings in the anemia associated with this disease. They reported granulocytopenia, thrombocytopenia, and normocytic anemia. They likened their findings to those of severe toxic aplasia such as that resulting from benzol.

### PATHOLOGY

Rosenthal<sup>2</sup> reported an extensive study of the pathology of the disease. He describes the pathological changes as occurring in three separate phases, the acute, subacute, and chronic. In the acute phase, the characteristic

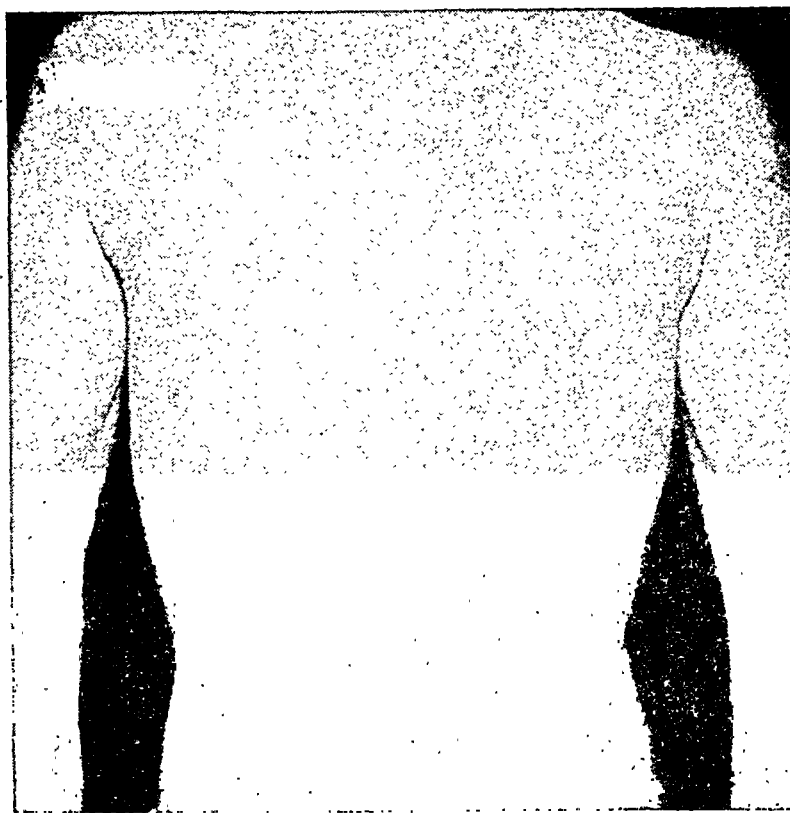


FIG. 3. Case C. C., widespread distribution of atypical lichen planus, demonstrating lichenification, follicular hyperkeratosis, "lace-work" scaling.

changes appeared to be thickening of the stratum corneum, widened hair follicles filled with keratin, acanthosis and marked cellular infiltration with polymorphonuclears, particularly eosinophiles. In the subacute phase there was further widening of the keratin layer. There was less inflammatory infiltration and some histiocytic infiltration. There was also degeneration of the stratum basalis. In the chronic phase the inflammatory reaction was less marked with only scattered inflammatory cells. The featured findings were an acanthosis, plugging of the hair follicles, and increased pigmentation in the basilar layer. This pigment stained with Becker's stain, a non-specific stain for melanin. Two cases of aplastic anemia were observed by Rosenthal,



one of which died of a cerebral hemorrhage after persistent granulocytopenia. The bone marrow in this case was hypoplastic. There was an associated subacute pancreatitis. Degenerative changes were found in the peripheral portion of the liver lobule. Isolated deposition of pigment in the liver was observed. This pigment also stained with Becker's stain and appeared to be the same as the pigment observed in skin with chronic lesions. Goldberg<sup>3</sup> described finding a pigment in the stroma of a biopsied lymph node. The liver presented a greenish fluorescence to ultra-violet ray despite the cessation of atabrine ingestion six months before.

### CLINICAL COURSE

Patients were kept under our own personal observation for varying periods up to as long as six months. Many of our patients were observed as out-patients, but the greater number were those referred for general hospital care and disposition from many different areas. It became evident as time went on that, with very few exceptions, those who were retained overseas did not show any material improvement. All of our patients who were to be evacuated to the United States were asked to write us after their arrival and report what was happening in so far as their skin lesions were concerned. These reports almost uniformly indicated that slow but steady improvement was to be expected after returning home. At least one patient reported the persistence of eruption as long as 12 months after evacuation from the theater. Though Dantzig and Marshall<sup>4</sup> and Goldberg<sup>3</sup> found no exacerbations of the cutaneous disease when atabrine was administered for a recurrence of malaria, we had a report from one patient who had several recurrences of malaria after leaving our hospital in New Guinea. All of his attacks of malaria were treated with quinine with the exception of one for which atabrine was administered. In the single instance when atabrine was given for his recurrence of malaria there was a severe coincidental exacerbation of the atypical lichen planus.

The hypertrophy of some of the individual lesions was so great that they gave the appearance of cutaneous horns. The nails of the fingers and toes became dystrophic, brittle, and separated from the nail beds. The regression of the individual lesions left in its wake an impermanent pigmentation of the skin and, less frequently, atrophic scarring.

The uninfected cases were afebrile.

From a therapeutic point of view, the cases most difficult to manage were those wherein there was an associated exudative process. Here the problem of nursing and medical care under rigors of tropical living and warfare were heavy. Secondary infection with resulting fever was common. In those instances where large body areas were denuded and exuded plasma, the maintenance of fluid balance and the correction of disturbances in blood chemistry in those patients who suffered severe plasma loss were probably as challenging a problem as any we met.

Of the several hundred cases treated and observed by us in the hospital for an average of six weeks only four showed signs of definite improvement over any significant period of time. All four had had their atabrine withdrawn prior to our being able to make this observation. Many others who likewise had had their atabrine withdrawn showed no improvement while they continued under our observation overseas.



FIG. 4. Case C. W., dystrophy of nails with loss of left index finger-nail. Note, too, the scalp lesions with alopecia areata.

No specific information on the mortality of this clinical triad is available in the literature reviewed. From what has been observed it appears that the mortality was very low and due to complications mentioned before, namely agranulocytosis, aplastic anemia and cerebral hemorrhage.

#### ETIOLOGY

It is reported<sup>1</sup> that Nisbet and Schmitt first suggested that atabrine might be the cause of this disease. Extensive skin patch-testing by us and

others with atabrine and/or 25 per cent ointment of atabrine in petrolatum gave positive reactions in only a few isolated instances. One would expect that if the disease were the effect of cumulative toxicity many cases would occur *after* the one year period. All of the cases observed by us bore a time relationship to the beginning of suppressive atabrine therapy and not to the arrival of the patients overseas or to their arrival in the tropics or in a particular geographic area. The one constant factor in all of the patients suffering from atypical lichen planus was the ingestion of atabrine in the usual suppressive dose of 0.1 gm. daily. We were unable to find one patient with atypical lichen planus who had been unfaithful in the taking of his atabrine, though this was apt to occur among some of the personnel despite the rigid enforcement of the suppressive use of the drug. There is much to suggest that in addition to a peculiar sensitivity to atabrine there may be one or more additional factors. Among those suggested have been sunlight, nutritional deficiency, and emotional tension. Patients almost uniformly looked and felt better after their hospitalization. In the hospital they received better nursing and medical care for their disease, rest, freedom from the hardships and emotional tension of combat, improved personal hygiene, and removal from the tropical sun. On the other hand, the disease occurred in non-combatant enlisted men and officers as often as in those who were in action. Many of the non-combatants were part of the complement of the very hospital in which they were admitted and treated as patients. These patients were never exposed to the physical and mental rigors of combat. Their food, as well as their facilities for personal hygiene, was unchanged by hospitalization.

In 10 of the first 150 patients that we studied a co-existing labial cheilosis was observed. This always responded to riboflavin administered orally in doses of 5 mg. daily. Coincidental with the disappearance of the cheilosis in two of these patients improvement in the atypical lichen planus was demonstrated. One of these patients had a severe progressive atypical lichen planus. While waiting for transfer to the United States, he developed a severe follicular tonsillitis. During the period of the tonsillitis, his skin condition became markedly worse and he developed, in addition, bilateral labial cheiloses and pressure decubiti over the sacrum, both iliac tuberosities, and medial epicondyles of both femora. On the basis of previously published experiments with riboflavin in decubiti,<sup>7</sup> riboflavin was administered. There occurred a disappearance of the cheilosis and the decubiti, and improvement for the first time in the atypical lichen planus. Continued improvement in his atypical lichen planus was observed for another six weeks when the patient was finally evacuated to the United States. We had hoped to pursue with suitable clinical experiments the possible relationship that might exist with disturbances in riboflavin metabolism as an intermediate step in the development of the disease. The opportunity to develop this phase in our investigation never came, and, as a result, it is mentioned here only as an

isolated observation. No other evidences of specific nutritional deficiency states appeared with significant regularity in our patients.

It was suggested that the subjective improvement or the slowing of the disease that often followed hospitalization might have been due to removal from the excessive exposure to tropical sun. As a basis for this, it has also been suggested that atabrine, a fluorescent acridine dye, might, in some individuals, produce a cutaneous photosensitivity. There is no actual proof to support this interesting hypothesis. One of our patients accepted the rôle of having one hand covered with a gauze bandage in which there had been

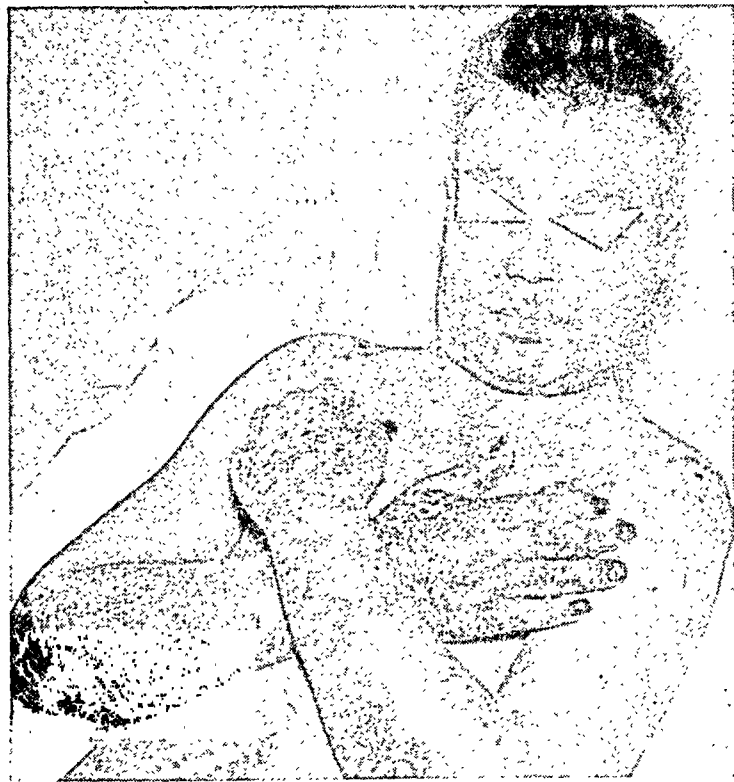


FIG. 5. Case F. E., generalized edema is present. This case of atypical lichen planus is associated with symmetrical exudative eczematoid features. Discoloration of skin and nails due to potassium permanganate.

incorporated some black paper. After six weeks, both the bandaged and unbandaged hand appeared to have progressed equally.

#### TREATMENT

All patients in whom a diagnosis of atypical lichen planus was made were evacuated to the United States regardless of the extent of the disease. This policy held as well for those patients who had an exfoliative dermatitis. Patients with the eczematoid dermatitis were sent back to duty if, under treatment, the eczematoid dermatitis disappeared and there were no evi-

dences of any lesions suggestive of atypical lichen planus. The rate of recurrence in this group was high, and many of the patients returned to duty had to be rehospitalized later on with the disease in an unresponsive and severe form or, as described earlier, accompanied by lesions of atypical lichen planus. The withdrawal of atabrine did not seem to offer these patients a chance to be cured if they were retained overseas. When we appreciated the rôle of atabrine in the disease, the drug was discontinued. While waiting for evacuation, treatment consisted of skilled nursing care, nutritious diets with liberal multi-vitamin supplements. Local therapy was administered only when exudation was present and this consisted exclusively of wet dressings or soaks. Solutions used for local application consisted of either boric acid, very dilute potassium permanganate, normal saline, or penicillin in saline (500 units per c.c.).

Parenteral penicillin was used in all cases that were grossly infected or in which fever was present.

Remarkable results can be reported from the administration of plasma in the severe exudative lesions regardless of whether or not demonstrable quantitative changes in the blood protein or albumin-globulin fractions existed. Blood plasma was used as often as once or twice a day. When there was an associated anemia of any significant degree whole blood was frequently given in addition to infusions of plasma. No instances of homologous serum jaundice occurred in our experience.

Some patients presented a generalized edema, often unassociated with hypoproteinemia or severe exudation. This edema responded remarkably to plasma infusions. Infrequently the edema was so marked that the only accessible vein for clasis was the external jugular.

The diets were as rich in protein as was possible, and this was supplemented with large amounts of gelatin served in iced fruit juices several times daily. In the exfoliative cases large doses of liver extract were administered intramuscularly as well.

A large hydrotherapy department<sup>8</sup> was maintained in order to provide tubs and basins for soaks and for the preparation of wet dressings. The extent of individual local treatment was solely dependent upon the degree of the exudative process that was going on.

No ointments were used by us in the tropics because it was apparent early that their use aggravated the skin conditions. Occasionally penicillin was used locally for secondary infection with good results but always in solution, excepting the very infrequent occasions when an ointment in a water-soluble base was employed for mild infection in small areas.

For sedation chloral or paraldehyde was used rather than barbiturates. For analgesia codeine was employed rather than salicylates. Arsenicals and bismuth used by others<sup>1</sup> were found not to affect the course of the disease. We had no experience in the use of heavy metals parenterally, nor did we employ radiation therapy in the management of any of our cases.

## SUMMARY AND CONCLUSIONS

1. The history of the disease, atypical lichen planus, was described, and its likely etiological relationship to a peculiar eczematoid dermatitis and a frequently occurring exfoliative dermatitis was discussed.

2. The clinical manifestations, pathology, and laboratory findings were described.

3. Prolonged ingestion of atabrine is considered to be the presumptive basic cause of the disease. Other factors, however, may be secondarily operative in its production.

4. It is the opinion of the author that atypical lichen planus is merely a cutaneous manifestation of a generalized systemic disorder.

5. Few instances of improvement were observed while the patients remained overseas. Because of this, plus the fact that the disease is both disabling and progressive, all patients with atypical lichen planus were evacuated to the United States.

6. Withdrawal of atabrine, and the maintenance of adequate nutrition were applied in all cases. Local therapy was found to be of only temporary value when exudation was present.

7. The value of infusions of plasma and whole blood in the management of the exudation and edema was stressed.

8. Penicillin is a valuable aid in treating those cases exhibiting secondary infection.

Photographs by 4th Med. Museum and Arts Dept., A. U. S.

## BIBLIOGRAPHY

1. Special Article, Evaluation of untoward reactions attributable to atabrine, *Bulletin U. S. Army Med. Dept.*, 1945, iv, 653-659.
2. ROSENTHAL, JULIUS: Atypical lichen planus, *Am. Jr. Path.*, 1946, xxii, 473-491.
3. GOLDBERG, L. C.: An unusual lichenoid dermatosis, *Jr. Am. Med. Assoc.*, 1946, cxxx, 775-781.
4. DANTZIG, LOUIS, and MARSHALL, L. E.: Tropical lichen planus—New Guinea variety, *New York State Jr. Med.*, 1946, xlii, 991-995.
5. EPSTEIN, IRVIN: The lichen planus eczematoid dermatitis complex of the Southwest Pacific, *Bull. U. S. Army Med. Dept.*, 1945, iv, 687-695.
6. MOST, HARRY, and HAYMAN, J. M.: Recovery from severe hypoplastic anemia associated with atypical lichen planus, *Bulletin U. S. Army Medical Dept.*, 1946, v, 339-342.
7. VORHAUS, M. G., GOMPERTZ, M. L., and FEDER, AARON: Clinical experiments with riboflavin, inositol, and calcium pantothenate, *Am. Jr. Digest. Dis.*, 1943, x, 45-48.
8. FEDER, AARON: Therapy unit for patients with skin diseases, *Bulletin U. S. Army Medical Dept.*, 1946, v, 343-345.

# CASE REPORTS

---

## PULMONARY EMBOLISM WITH ACUTE COR PULMONALE AND EXTREMELY RAPID VENTRICULAR RATE IN A YOUNG, ACTIVE, APPARENTLY HEALTHY ADULT \*

By WILLIAM F. RENNER, M.D., *Baltimore, Maryland*

THE problem of venous thrombosis with associated pulmonary embolism has received much attention in the medical literature of recent years. The great bulk of the literature has dealt with venous thrombosis of the secondary or complicating type, that is, venous thrombosis complicating surgery or delivery or occurring in the course of infectious disease or non-infectious systemic disease, particularly cardiac disease with congestive failure. Despite a number of excellent reports on the subject, it is not sufficiently well recognized that venous thrombosis with pulmonary embolism does occur in individuals who have not experienced recent surgery or childbirth, who do not have varicose veins, who have no apparent infectious or non-infectious disease, and who, at the time embolism occurs, are leading a normal active life. In 1945 Hampton, Prandoni, and King reported 10 cases of pulmonary embolism seen in Army personnel at Walter Reed General Hospital, occurring in each case while the individual was at work with no history of cardiac disease or of known phlebitis. The transfer diagnoses in these cases included coronary occlusion,<sup>1</sup> pneumonia, angina pectoris, pericardial effusion, and metastatic carcinoma of the lungs. In no case had the correct diagnosis been made prior to admission to Walter Reed Hospital.

The lack of appreciation by many physicians that venous thrombosis and pulmonary embolism do occur in active otherwise apparently healthy adults and the occurrence of several unusual features in a case recently observed by us are the justification for this report. The patient was referred to The Union Memorial Hospital as a case of paroxysmal tachycardia. Pulmonary embolism was not considered until several hours after admission when further developments and a careful detailed history pointed to venous thrombosis and pulmonary embolism as the underlying disorder. The extremely rapid ventricular rate of 300 to 315 beats per minute is, we believe, the fastest reported in an adult. The presence of a significant autoagglutinin titer raises the question of the possible etiologic significance of this factor in this case.

### CASE REPORT

The patient was a 32 year old white salesman for a pharmaceutical company, who was admitted on the House Service, Union Memorial Hospital, December 10, 1947, with the chief complaint of a fainting attack followed by palpitation, four and one-half hours previously. There was nothing of importance in the patient's past

\* Received for publication March 30, 1948.

Case from the House Service, Union Memorial Hospital.

history except that since discharge from the Army several years previously he had been imbibing alcoholic beverages heavily. This is mentioned because it is the impression of some that idiopathic venous thrombosis and pulmonary embolism are more common in chronic alcoholics.<sup>12</sup> Review by systems was completely negative except for the information that the patient had had frequent colds during the past winter, the last one six weeks prior to admission.

On December 9, 1947, the patient went to bed at 9 p.m. feeling as usual except that his feet felt unusually cold, for which reason he wore a pair of socks to bed. For three weeks previous, the patient had noticed some stiffness and soreness in his calf muscles upon arising in the morning, which would disappear when he became active. He attributed these symptoms to playing football with his young children during the preceding month. He had noticed no stiffness or soreness in the thighs. The patient arose at 6:30 a.m. December 10 and went downstairs to his desk to work on some company reports. He had been working about 10 minutes when he suddenly became weak and broke into profuse perspiration. He went to the kitchen, wiped off his face, then returned to his desk. A few minutes later he had a chilly

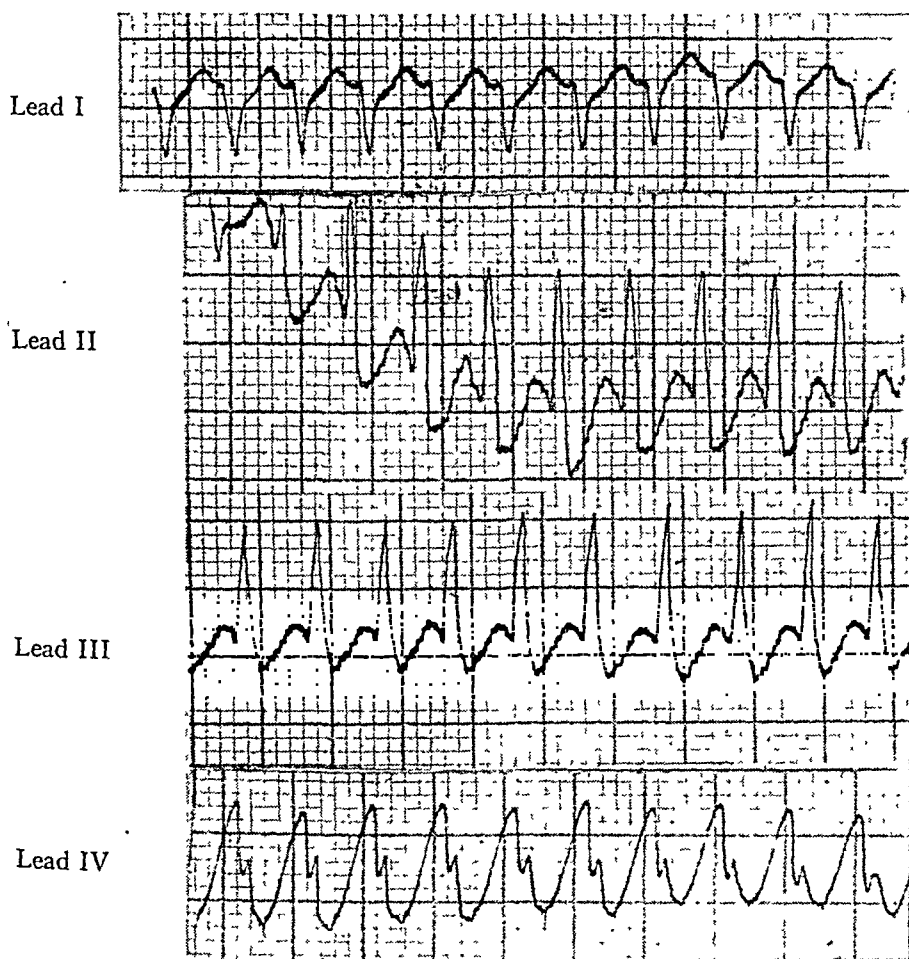


FIG. 1. Electrocardiogram taken two hours after fainting attack and one hour after onset of tachycardia. Rate is 300 to 315 per minute. Note the extreme right axis shift. Because of the extremely rapid rate and the absence of a period of electrical quiescence in the auricles in all leads, the rhythm is interpreted as auricular flutter with 1:1 conduction, although supraventricular tachycardia can not be definitely ruled out. (Compare with figure 2.)



sensation but did not shake, became dizzy, his vision became blurred, and he fell to the floor. He estimates that he was unconscious 5 to 10 minutes. He then crawled on hands and knees upstairs to his bedroom and into bed. Fifteen minutes later, while lying in bed, he noted the onset of rapid forceful beating of his heart followed by mild to moderate dyspnea. An hour later the family physician arrived and took an E.K.G. which showed a ventricular rate of 300 to 315 and a marked right axis shift (figure 1). The patient was given morphine and one cat unit of digifolin parenterally. Various types of vagal stimulation were tried without success. Just before entering the ambulance the patient vomited once. En route to the hospital he noted that his dyspnea had disappeared and that his heart no longer was beating rapidly.

Physical examination immediately upon admission to the hospital was essentially negative. The heart rate was normal. No murmurs were heard, the heart did not appear enlarged, the lungs were clear to auscultation and percussion. The diagnosis of paroxysmal tachycardia was concurred in.

Three to four hours after admission the patient became slightly dyspneic and complained of a sharp pain in the precordial area, radiating to the right chest and to the midscapular area and made worse by deep inspiration. Upon going into the history carefully, it was learned that this pain had come on about an hour after the onset of the tachycardia and had persisted in a dull form up to the present when it had become again accentuated. A cough was now present; no blood was present in the sputum. Physical examination at this time revealed the presence of a short rough sound just to the left of the sternum in the third interspace which was synchronous with systole and which was interpreted to be a pleuro-pericardial friction rub. A loud pleural friction rub was heard anteriorly to the right of the mediastinum at the level of the fourth interspace and extending horizontally to the posterior aspect of the left chest over the left upper lobe. A friction rub was heard also in the left lower axillary area. A few fine crackling râles were heard at both lung bases. Examination of the legs revealed definite tenderness in both calves and a questionably positive Homan's sign on the right. Varicosities were not present.

*Laboratory:* The white blood cell count on admission was 8,000 with 71 per cent polymorphonuclear cells. Hemoglobin was 89 per cent. Sedimentation rate was 33, uncorrected. An electrocardiogram taken one hour after admission and three and one-half hours after that taken in the patient's home (i.e. four and one-half hours after onset of tachycardia) showed a normal sinus rhythm and a normal axis (figure 2). The rapid reversion of the axis back to normal was in itself considered strong evidence of pulmonary embolism. A third electrocardiogram on the third hospital day showed no important change from the second. A roentgen-ray taken on the day after admission showed perfectly clear lung fields. A repeat film taken on the second day after admission gave evidence of a small embolus in the right base and opposite the fourth right rib anteriorly and the sixth interspace posteriorly. A roentgenogram on the third day after admission showed a reticular density in the outer portion of the mid right lung field, probably due to multiple emboli. The lesion in the right base had cleared. An autoagglutinin titer done one week after admission showed macroscopic clumping out to a dilution of 1:80 (4 plus, 3 plus, 2 plus, 1 plus). An autoagglutinin titer seven weeks later was positive only in a 1:10 dilution (1 plus).

*Course:* The patient was started on heparin and Dicumarol on the day of admission. On the second day of hospitalization the patient's temperature, which was normal on admission, rose to 101.6° F., returning to normal on the sixth hospital day. After the second hospital day the patient was asymptomatic. A chest plate on the tenth hospital day showed clear lung fields.

*Comment:* Although it is well recognized that pulmonary embolism may precipitate a paroxysmal arrhythmia, certainly the average physician confronted

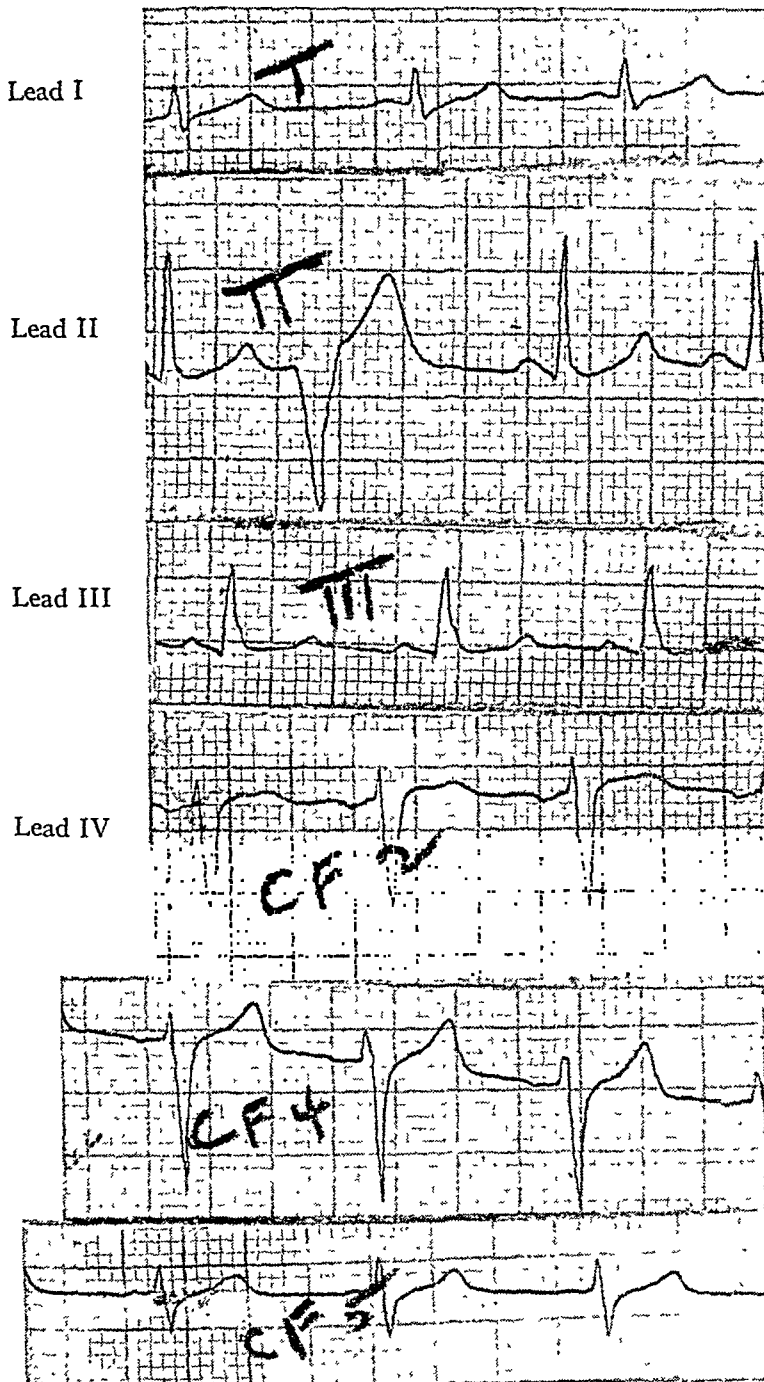


FIG. 2. Electrocardiogram taken four and one-half hours after the tracing shown in figure 1. Sinus rhythm is now present with a rate of 88. Note the marked shift of the axis back to normal, in itself strongly pointing to pulmonary embolism.

with a case of paroxysmal tachycardia in an apparently normal individual is likely to overlook this possibility. The high index of suspicion essential to the diagnosis of many cases of pulmonary embolism must include the paroxysmal arrhythmias. Approximately 300 beats per minute has been considered the upper limit at which the human heart can pulsate. Lyon, in reporting a rate of 313 in a four and one-half week old infant in 1937, reviewed the literature on excessively rapid rates.<sup>13</sup>

He was able to find 16 cases with a rate over 280, ten of which were confirmed graphically. A ventricular rate of 300 was recorded by electrocardiogram in four cases, two of which were in adults. In no case was an electrocardiogram published which showed a rate that exceeded 300 per minute. Katz and White both refer to a rate of 345 in a 10 day old infant as the fastest recorded rate.<sup>11, 18</sup>



FIG. 3. Chest roentgenogram on the day after attack. Note the dilated heart as compared with figure 5. The lungs were interpreted by the roentgenologist as clear.

To our knowledge, the rate of 300 to 315 in the patient who is the subject of this report is the fastest ventricular rate recorded in a human beyond infancy. The rhythm is considered to be auricular flutter with 1:1 conduction.

The etiology of venous thrombosis is still poorly understood. There are three factors which are generally considered important: (1) a local, traumatic, infectious, toxic or preëxisting lesion of the vein wall, (2) relative stasis of the venous blood flow, and (3) changes in the composition of the blood. With re-

gard to the third factor, no single constant abnormality of the blood has been found which can be held responsible in all cases. In the subject of this report local trauma must be considered since the patient was a chronic alcoholic and since he gave a history of playing football with his children for a month prior to his attack. However, he could recall no instance of trauma. Venous stasis may have played a rôle in a patient who occasionally slept cramped in the back seat of his automobile after an alcoholic debauch. In view of the fact that extensive



Fig. 4. Chest roentgenogram three days after attack. A reticular density is present in the outer portion of the mid-right lung, suggesting multiple small emboli.

venous thrombosis has been reported in some cases of primary atypical pneumonia with high cold or autoagglutinin titers and in view of the fact that venous thrombosis is thought to be more common in the spring and winter months when respiratory infections are frequent and more common in the northern clinics than in the southern, an autoagglutinin titer was run one week after admission.<sup>16, 17</sup> The titer was 1 : 80 (4 plus, 3 plus, 2 plus, 1 plus), the end point being determined by the presence of macroscopic clumping. Although 1 : 80 is not a very high titer,

it is significant according to the work of Finland et al. at Boston City Hospital.<sup>17</sup> Of 100 patients with no disease examined by these workers, none had an autoagglutinin present in significant titer, that is 1:40 or greater. Of 851 patients with various diseases other than primary atypical pneumonia and hemolytic anemia, only 1.2 per cent had autoagglutinins present in significant titer. A titer run on the subject of this report seven weeks after the first was 1:10 (1 plus). The



FIG. 5. Chest roentgenogram ten days after attack. Lungs are now clear. Heart has decreased markedly in size. (Compare with figure 3.)

question arises as to whether this patient had a rise in his autoagglutinin titer coincident with one of the frequent respiratory infections to which he is subject and whether such a rise played any rôle in the occurrence of his venous thrombosis and pulmonary embolism. It is of interest that DeTakats has observed, "atypical pneumonia seems to predispose to clotting" of the blood.<sup>18</sup> In an effort to demonstrate activity of the autoagglutinins, one of the patient's hands was immersed

in ice water for one to two minutes. No unusual color change was noted. However, it was noted that, whereas the temperature of the hands of two controls returned promptly to normal, the patient's hand which had been immersed in ice water was distinctly cooler than his other hand one half hour later, and some of the fingers were distinctly cooler than others. We feel that no definite significance can be attached to this.

### SUMMARY

1. A case of pulmonary embolism in an active apparently healthy young adult is reported. The high index of suspicion essential to the diagnosis of many cases of pulmonary embolism must include the paroxysmal arrhythmias even in apparently healthy individuals.

2. The ventricular rate of 300 to 315 beats per minute is, we believe, the fastest recorded in a human heart beyond infancy.

3. The possible etiologic significance of cold or autoagglutinins in this case is briefly discussed.

### BIBLIOGRAPHY

1. ALLEN, E. V., BARKER, N. W., and HINES, E. A.: *Peripheral vascular diseases*, 1946, W. B. Saunders Co., Philadelphia, Pa.
2. BARKER, N. W.: Primary idiopathic thrombophlebitis, *Arch. Int. Med.*, 1936, lviii, 147.
3. BAUER, G.: Venous thrombosis, *Arch. Surg.*, 1941, xliii, 462.
4. BRIGGS, J. B.: Recurring phlebitis of obscure origin, *Bull. Johns Hopkins Hosp.*, 1905, xvi, 228.
5. DETAKATS, G., and FOWLER, E. F.: The problem of thrombo-embolism, *Surgery*, 1945, xvii, 153.
6. FLEISCHNER, F., HAMPTON, A. O., and CASTLEMAN, B.: Linear shadows in the lung, *Am. Jr. Roentgenol. and Rad. Therapy*, 1941, xlvii, 610.
7. HAMPTON, A. O., and CASTLEMAN, B.: Correlation of postmortem chest teleoroentgenograms with autopsy findings with special reference to pulmonary embolism and infarction, *Am. Jr. Roentgenol. and Rad. Therapy*, 1940, xliii, 305.
8. HAMPTON, A. O., PRANDONI, A. G., and KING, J. T.: Pulmonary embolism from obscure sources, *Bull. Johns Hopkins Hosp.*, 1945, lxxvi, 245.
9. HOMANS, J.: Pulmonary embolism due to quiet venous thrombosis, *New England Jr. Med.*, 1943, ccix, 309.
10. JORPES, J. E.: Origin and physiology of heparin, *Ann. Int. Med.*, 1947, xxvii, 361.
11. KATZ, L. N.: *Electrocardiography*, 1946, Lea & Febiger Co., Philadelphia, Pa.
12. KING, J. T.: Personal communication.
13. LYON, J. L.: Excessively rapid heart rates, *Jr. Am. Med. Assoc.*, 1937, cviii, 1393.
14. MEILMAN, E., and DAVISON, S.: Pulmonary embolism of non-cardiac and non-post-operative origin, *Jr. Mt. Sinai Hosp.*, 1944, ii, 164.
15. MURNAGHAN, D., MCGINN, S., and WHITE, P. D.: Pulmonary embolism with and without cor pulmonale, *Am. Heart Jr.*, 1943, xxv, 573.
16. OCHSNER, A.: Intravenous clotting, *Surgery*, 1945, xvii, 240.
17. RENNER, W. F., and MCSHANE, J. R.: The rôle of autoagglutinins in hemolytic anemias, *South. Med. Jr.*, 1947, xl, 973.
18. WHITE, P. D.: *Heart disease*, 1946, The Macmillan Co., New York, N. Y.

## PARAPLEGIA SECONDARY TO METASTATIC PROSTATIC CARCINOMA TREATED WITH STILBESTROL: REPORT OF A CASE\*

By ISIDORE S. EDELMAN, M.D., *Boston, Massachusetts*

### INTRODUCTION

TRANSVERSE interruption of spinal cord function occurs relatively infrequently as a result of metastases from carcinoma of the prostate. Bumpus<sup>1</sup> reported that 11 of 1,000 untreated patients with carcinoma of the prostate had symptoms simulating tumor of the cord with some paralysis prior to death. In those patients with cord compression by metastatic tumor and loss of motor power, loss of sphincteric control and associated ascending urinary tract infection, palliation becomes a problem of prime importance.

The beneficial palliative effects of orchiectomy and/or estrogenic therapy in the treatment of advanced prostatic carcinoma are well known.<sup>2, 3, 4, 5, 6</sup> However, the response of neurologic complications to this type of therapy has been observed less frequently. In at least five cases previously reported, considerable relief was obtained by hormonal therapy.<sup>4, 5, 9, 10</sup> The following is an additional case of this kind.

### CASE REPORT

The patient, a 66 year old white male, was admitted to this hospital on June 24, 1947 because of generalized weakness and pain in the region of the right ischium. His symptoms began approximately six months prior to admission with severe lower abdominal cramps and anorexia. During the next four months, he developed urinary frequency, urgency and dysuria. He had been admitted to another hospital in May 1947, where the prostate was found to be hard, fixed and enlarged. Roentgen-ray examination revealed a left pleural effusion and metastatic involvement of the vertebrae, ribs, skull and pelvis. A transurethral resection of the prostate was performed because of urinary retention. The pathological report on the tissue obtained was "adenomatoid hyperplasia of the prostate." There had been a weight loss of 40 pounds. The patient was transferred to this hospital for further care.

Physical examination revealed an emaciated and pale elderly male. His blood pressure was 110 mm. Hg systolic and 65 diastolic. The pulse rate, respiratory rate and temperature were all normal. The only findings of note were tenderness over the hips, pitting edema of both ankles and a stony hard, asymmetrically enlarged prostate. The neurological examination was negative except for increased deep tendon reflexes in all extremities.

On admission, the laboratory findings of significance were an alkaline phosphatase of 22.7 Bodansky units, an acid phosphatase of 5.0 Gutman units, a red blood count of 2.38 million cells per cu. mm. and a hemoglobin of 7.9 grams. The sternal marrow was found to be aplastic and to contain tumor cells in clumps. Serum Kahn, blood urea nitrogen, fasting blood sugar, total plasma proteins, and urinalysis were all within normal limits. The urine was negative for Bence-Jones protein on three occasions. An electrocardiogram showed left axis deviation. Roentgen-ray examination of the skull revealed a 2 cm. isolated zone of radiolucency in the parietal region. Extensive osteoblastic changes were noted throughout the dorso-lumbar spine, ilia and sacrum. Rarefactive areas were seen in the pubis and ischium. Sev-

\* Received for publication February 7, 1948.

From the division of Neoplastic Diseases, Montefiore Hospital, New York, N. Y.

eral of the lower ribs showed sclerotic changes and the left costophrenic sinus was obliterated. Intravenous pyelography was negative except for a large oval filling defect in the floor of the bladder presumed to be due to an enlarged prostate. Barium enema and gastrointestinal series were essentially negative.

On July 18 an acid phosphatase of 12.0 G.U. and on August 1, one of 10.2 G.U. were reported. A diagnosis of carcinoma of the prostate with extensive bony metastases was made and the patient was started on pituitary irradiation as an experimental procedure. From July 31 to August 19, the patient received 3,000 roentgens delivered by cross-firing through three fields to the pituitary gland. The patient failed to improve. He complained of increasing pain in the hips and low back. On August 28, weakness of the legs was noted. By the September 2, a marked paraparesis of the lower extremities and an absence of pain perception corresponding to a level of D-8 had developed. In addition, marked hyperreflexia at the knees and ankles with ankle clonus and positive Babinski signs bilaterally were found. Lumbar puncture performed at L 4-5 showed considerable block. As can be seen from figure 1, there was a prompt rise in spinal fluid pressure on applying abdominal pressure but practically

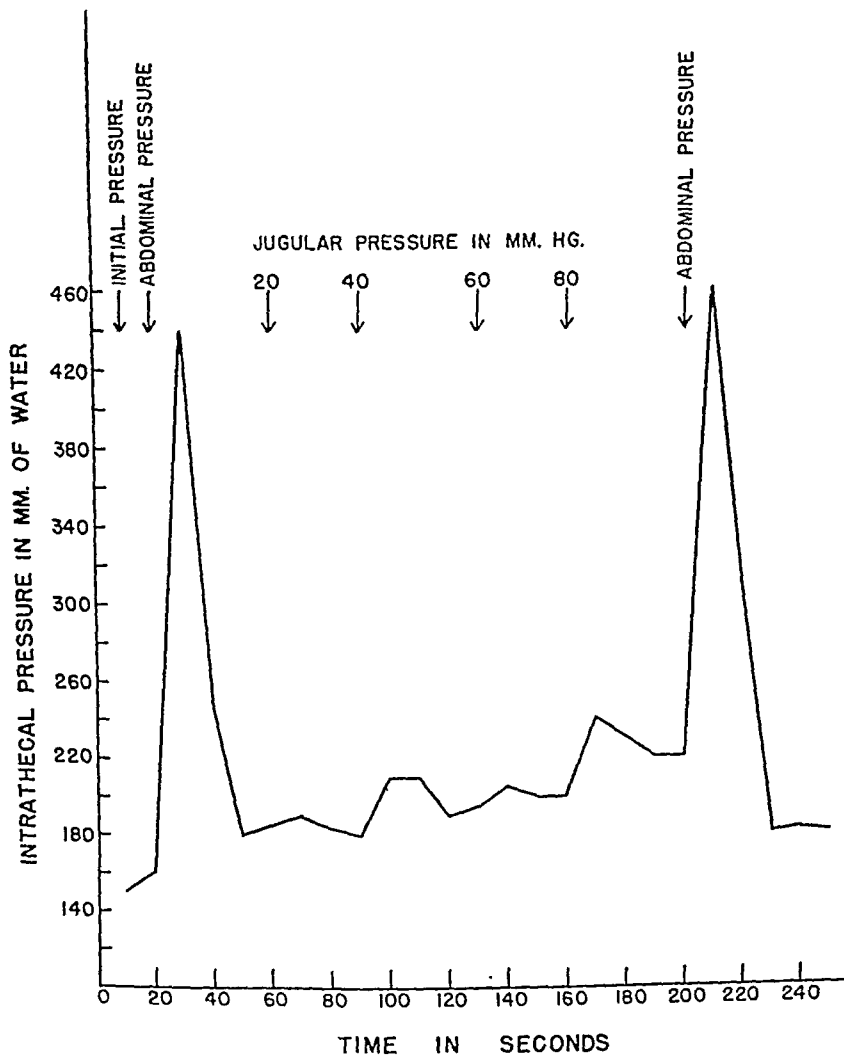


FIG. 1. September 3, 1947. Incomplete block prior to stilbestrol therapy. Spinal fluid manometrics measured with a water manometer and pressure applied by a sphygmomanometer with the cuff around the neck.



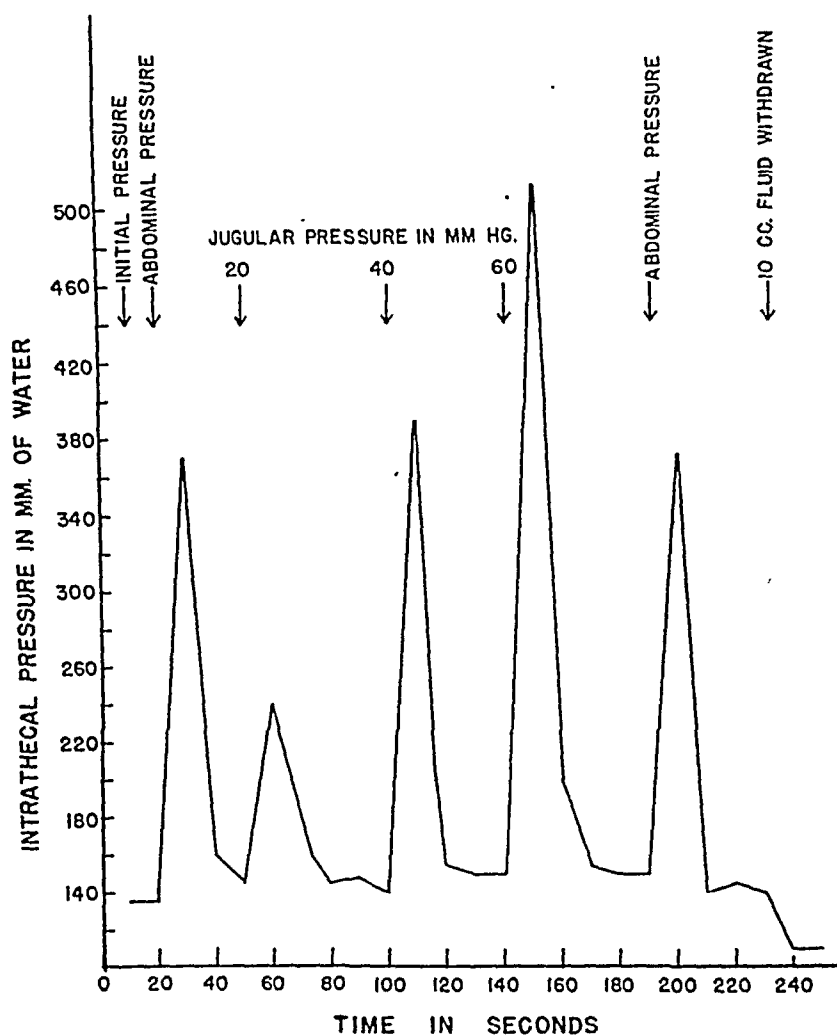


FIG. 2. October 14, 1947. Open manometrics after stilbestrol therapy. Spinal fluid manometrics measured with a water manometer and pressure applied by a sphygmomanometer with the cuff around the neck.

no rise when the neck veins were compressed by means of a sphygmomanometer cuff raised to a pressure as high as 80 mm. of mercury. These findings are consistent with a partial block to the free circulation of spinal fluid. Examination of the fluid revealed xanthochromia, a 1 plus Pandy reaction, a protein of 170 mg. per cent and only a few cells. Roentgen-rays of the dorsal spine failed to show collapse of any of the vertebral bodies. A neurosurgical consultation was obtained, and it was felt that laminectomy for decompression was not indicated. By September 5 the paraparesis progressed to a paraplegia and the patient was started on 15 mg. of stilbestrol per day. Ten days later the patient began to have a return of motor power in his legs. By September 26 he had a return of pain perception and could move his legs almost perfectly. On September 29 his acid phosphatase decreased to 0.2 G.U. A lumbar puncture performed on October 14 yielded normal manometrics. As contrasted to figure 1, it can be seen from figure 2 that there is an immediate and sharp rise in intra-theal pressure with pressure applied around the neck of 20, 40 and 60 mm. of mercury. In addition, the prompt fall in spinal fluid pressure to base levels on removal of neck pressure is indicative of an unobstructed spinal fluid circulation. At this time, the patient had relief of pain, a decrease in anorexia and a striking increase in his feeling

of well-being. The patient could stand but not walk unassisted. Ankle clonus and the positive Babinski persisted. On digital rectal examination there seemed to be a decrease in the size of the prostate. The patient was discharged on October 30, 1947. He was seen on November 5, 1947 and continued to be improved.

### DISCUSSION

The diagnosis of prostatic malignancy was based on the physical characteristics of the gland, the fairly typical osteoblastic metastases and acid phosphatase values above 10 units. The striking therapeutic response to estrogenic therapy and fall in the acid phosphatase values to normal supports the diagnosis. Although other conditions can give small increases in serum acid phosphatase levels, a value greater than 10 units is considered to be diagnostic of prostatic carcinoma.<sup>9</sup>

The pathogenesis of the paraplegia seems to be fairly clear. The clear cut evidence of a spinal fluid block without collapse of any of the vertebral bodies indicates that a soft tissue mass was compressing or invading the spinal cord. That this mass was metastatic from the prostate is supported by the considerable symptomatic relief, the open manometrics and return of spinal fluid protein to normal, with stilbestrol therapy.

TABLE I  
Pertinent Laboratory Data before and after Stilbestrol Therapy

	Alkaline Phosphatase Bodansky Units	Acid Phosphatase Gutman Units	Spinal Fluid Protein
7/18/47	16.8	12.0	170 mg. %
8/ 1/47	16.6	10.2	
8/28/47	Onset of Paraplegia		
9/ 4/47			
9/ 5/47	Stilbestrol Therapy Started		
9/29/47	17.7	0.2	31 mg. %
10/13/47	22.8	1.7	
10/14/47			

The time relations and chemical changes indicated in the above table suggest that the relief of the neurologic symptoms came about as a direct result of an inhibiting effect of stilbestrol on the tumor growth in the spinal canal.

Clarke and Viets<sup>10</sup> reported a very similar case with objective evidence of relief of a spinal fluid obstruction. As far as we know this is the second time that objective evidence of relief of a block within the spinal canal by hormonal therapy has been demonstrated. Of greater importance, however, is the palliative effect obtained. In this instance, a patient with advanced and widespread cancer, with severe pain, completely bed-ridden and paralyzed from the waist down, was enabled to leave the hospital free of pain and able to move his legs.

### SUMMARY

A case of paraplegia secondary to metastases from a carcinoma of the prostate is reported. Relief of symptoms and of a spinal fluid block occurred after administration of stilbestrol. The importance of palliation in this type of case is stressed.

## BIBLIOGRAPHY

1. BUMPUS, H. C., JR.: Carcinoma of the prostate, Surg., Gynec. and Obst., 1926, xliii, 150-155.
2. HERGER, C. C., and SAUER, H. R.: A consideration of the effect of androgen control treatment of carcinoma of the prostate, N. Y. State Jr. Med., 1947, xlvii, 494.
3. DEMING, C. L.: The hormonal treatment of prostatic malignancy, Bull. N. Y. Acad. Med., 1946, xxii, 88.
4. NESBIT, R. M., and CUMMINGS, R. H.: Prostatic carcinoma treated by orchiectomy, Jr. Am. Med. Assoc., 1942, cxx, 1109.
5. HUGGINS, C.: Prostatic cancer treated by orchiectomy: the five year results, Jr. Am. Med. Assoc., 1946, cxxxi, 576.
6. NESBIT, R. M.: Cancer of the prostate: general considerations, N. Y. State Jr. Med., 1947, xlvii, 376.
7. YOUNG, H. A.: The cure of cancer of the prostate by radical perincal prostatectomy, Jr. Urol., 1946, liii, 188-256.
8. GUTMAN, A. B.: Serum acid phosphatase in patients with carcinoma of the prostate gland, Jr. Am. Med. Assoc., 1942, cxx, 1113.
9. WRAY, S.: Blood acid phosphatase in prostatic cancer, The Lancet, 1945, i, 783.
10. CLARKE, B. G., and VIETS, H. R.: Effect of diethylstilbestrol on neurologic symptoms of carcinoma of the prostate, Jr. Am. Med. Assoc., 1943, cxxi, 499.

---

 HYPERSENSITIVITY TO FOLIC ACID \*

By DANA C. MITCHELL, M.D., R. W. VILTER, M.D., F.A.C.P., and C. F. VILTER, M.D., *Cincinnati, Ohio*

SYNTHETIC folic acid (pteroyl glutamic acid) has been used extensively in clinical investigation since November 1945 following reports of its effectiveness in the anemia of pernicious anemia, sprue and nutritional macrocytic anemia.<sup>1,4</sup> It has been available for general use during the past years and although it has been helpful in controlling the anemia of persons with pernicious anemia who developed hypersensitivity reactions to liver extract, it has failed to prevent the neurologic complications of pernicious anemia.<sup>5</sup> Up to the time of writing hypersensitivity reactions to folic acid have not been noted though some persons who have received between 50 and 250 mg. intravenously have complained of flushing and tingling sensations in the face and extremities and other unpleasant vasomotor symptoms.<sup>3</sup>

Recently we have observed a patient who developed maculopapular dermatitis during a course of folic acid given orally and a severe anaphylactoid reaction later following the intravenous administration of 50 mg. The case is being reported since we are not aware that a similar reaction has occurred following the administration of folic acid.

## CASE REPORT

A 35-year-old white woman was admitted to the Medical Service of the Cincinnati General Hospital on April 17, 1947 with a diagnosis of granulocytopenia which had followed the administration of thiouracil. The patient had been treated in the

\* Received for publication August 18, 1947.

From the Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Out-Patient Dispensary for thyrotoxicosis and thyrotoxic heart disease since April 1943. Three courses of thiouracil had been administered during this time with a reduction in basal metabolism and temporary improvement in cardiac function. On April 24, 1946 the patient had developed a mild leukopenia during one of the courses of thiouracil and was given 5 mg. folic acid orally three times a day in an attempt to combat it. She took both thiouracil and folic acid for two weeks. When, however, a maculopapular erythematous and pruritic rash appeared over her anterior chest wall and the extensor surfaces of both forearms, she discontinued the folic acid. Within 36 hours the pruritus disappeared and the skin rash had begun to clear even though she was still taking thiouracil. Later the thiouracil was discontinued since the leukopenia persisted and the thyrotoxic symptoms had abated. On April 3, 1947 thiouracil therapy was reinstituted, 0.2 gram three times a day because of recurrent thyrotoxic manifestations. On April 14, 1947 she noted a severe sore throat and an itching maculopapular rash over the arms and shoulders. She discontinued the thiouracil, the rash began to clear but the throat became progressively more painful.

The patient's past history did not reveal any suggestion of allergic tendencies until about three years before admission. At this time she developed recurrent generalized maculopapular eruptions which she attributed to the ingestion of tomatoes, pork or oranges, to contact with woolen blankets, many common soaps and most face powders. During a previous hospitalization she had developed dermatitis following the administration of phenobarbital and an erythematous pruritic rash and shortness of breath shortly after the administration of nembutal and aspirin.

The patient was acutely ill, her temperature was 104° F. and her pharynx was fiery red, edematous and covered with purulent exudate particularly over the tonsils. She had difficulty in swallowing, moderate trismus, and mild cardiac failure with auricular fibrillation. The white blood cell count was 2000 and the differential count 96 per cent lymphocytes and 4 per cent monocytes. The bone marrow showed 9 per cent myeloblasts but no more mature granulocytes. The erythrocyte series was essentially normal and megakaryocytes were present in normal numbers.

During the first week her temperature ranged between 101 and 104°. Penicillin and general supportive measures were ineffective in controlling the throat infection. Since the patient's course was steadily downward and since she showed no evidence of recovery of myeloid elements in the peripheral blood, all types of reputed bone marrow stimulants were given consideration. Folic acid was selected because there had been no reports of hypersensitivity reactions following its administration even though the evidence from the literature and our own experience did not indicate that it would be effective in this type of toxic granulocytopenia.<sup>2</sup> She was given one dose of 50 mg. of synthetic folic acid intravenously on April 24, 1947. There was no objective reaction to this initial injection but the patient stated later that she had noted slight flushing of the face and dizziness. On the following day a second dose of 50 mg. synthetic folic acid was administered intravenously. Immediately after the injection had been completed the patient suddenly became dyspneic, orthopneic, and extremely anxious. She sat up in bed, grasped her chest, and complained of severe substernal oppression. Her face became fiery red, then a livid purple. The pulse rate became extremely rapid (170 to 190 beats per minute) and could not be palpated at the wrist. Her respirations increased to 40 per minute. Blood pressure readings were not taken. The extreme dyspnea and orthopnea lasted about five minutes. Thereafter breathing became easier and orthopnea gradually disappeared. After 10 minutes the patient was able to lie back in bed and the cyanosis of the face had decreased.

Two days following this reaction and again 16 days later intradermal skin tests were carried out with the original solution of folic acid (No. 1) which had produced the reaction and similar material from a second stock bottle of folic acid (No. 2).

In the first test the control solution was physiologic saline and in the second, a 1 per cent solution of sodium bicarbonate, the solute for the folic acid. In both instances positive skin reactions were obtained to the solutions containing folic acid (table 1). Attempts to demonstrate precipitins for folic acid in the patient's serum were unsuccessful.

The patient remained critically ill until April 30, 1947 in spite of the use of both penicillin and streptomycin. Thereafter her temperature fell, infection cleared and bone marrow studies revealed an increase in myeloid elements with maturation arrest at the B myelocyte stage. On May 3, 1947, the sixteenth hospital day, 21 per cent

TABLE I

Reaction to Intradermal Tests with Folic Acid and Solutions of Physiologic Saline and Sodium Bicarbonate

April 27, 1947	5 minutes	10 minutes	15 minutes
Folic acid No. 1	Erythema, 3.5×2 cm.	Erythema, 3.5×4 cm. with pseudopods	Erythema 3.5×3 cm., pseudopods receding
Normal saline	Negative	Negative	Negative
May 13, 1947	5 minutes	10 minutes	15 minutes
Folic acid No. 1	Erythema, 2.5×3.5 cm.	Erythema, 3.5×3.5 cm. with pseudopods	Erythema, 2.5×1.75
Folic acid No. 2	Erythema, 2.5×4 cm.	Erythema, 2.5×4 cm., large pseudo- pods	Erythema, 2.5×2.25
1% sodium bicarbonate solution	Negative	Negative	Negative

young polymorphonuclear leukocytes were found in the peripheral blood. From that time on her recovery was rapid. Polymorphonuclear leukocytes returned to normal and the patient was discharged in good condition on June 4, 1947.

### SUMMARY

An instance of a severe anaphylactoid reaction following the intravenous administration of folic acid is reported. The patient had a history of sensitivity to many common drugs and had had an episode of dermatitis following a previous course of folic acid administered orally. Sensitization is presumed to have occurred at this time.

Such a reaction to folic acid must be quite rare since the drug has been administered orally and parenterally many times in the last few years without a report of a similar reaction.

### BIBLIOGRAPHY

1. DARBY, W. J., and JONES, E.: The treatment of sprue with synthetic *Lactobacillus casei* factor (folic acid, vitamin M), Proc. Soc. Exper. Biol. and Med., 1945, 1x, 259.
2. DAVIDSON, L. S. P., and GIRDWOOD, R. H.: Folic acid as a therapeutic agent, British Med. Jr., 1947, i, 587.

3. DOAN, C. A.: Folic acid (synthetic *L. casei* factor), an essential panhematopoietic stimulus. Experimental and clinical studies, *Am. Jr. Med. Sci.*, 1946, ccxii, 257.
  4. SPIES, T. D., VILTER, C. F., KOCH, M. B., and CALDWELL, M. H.: Observations in the antianemic properties of synthetic folic acid, *South. Med. Jr.*, 1945, xxxviii, 707.
  5. VILTER, C. F., VILTER, R. W., and SPIES, T. D.: The treatment of pernicious and related anemias with synthetic folic acid. I. Observations on the maintenance of a normal hematologic status and on the occurrence of combined system disease at the end of one year, *Jr. Lab. and Clin. Med.*, 1947, xxxii, 262.
- 

## DIAGNOSTIC FEATURES OF SPLENIC CYSTS WITH CASE REPORT AND REVIEW OF THE LITERATURE \*

By ARTHUR A. FISCHL, M.D., F.A.C.P., and JEAN PAPPS, M.D.,  
*Jamaica, L. I., N. Y.*

SPLENIC cysts occur infrequently in the human body. They were first mentioned by Andral<sup>1</sup> in 1829 in an autopsy report. Pemberton,<sup>2</sup> in a review of splenectomies at the Mayo Clinic, found four cysts in 800 cases. Sweet<sup>3</sup> more recently reviewed the literature and observed 148 cases of all varieties of cysts up to 1941. This low incidence is no doubt the cause of our paucity of knowledge regarding the clinical features. After reviewing the literature and comparing the essential findings of our case with those reported, we were impressed, however, with the remarkable similarity of the clinical and roentgenological pictures of splenic cysts. The diagnostic features are usually quite evident and afford a basis for a preoperative diagnosis. Discussion of the findings in the case here reported will serve as a general review of this subject.

### CLASSIFICATION

Several classifications of cysts have been outlined. Of these many are confusing and offer little aid to the clinician. McClure and Altmeier<sup>4</sup> divide them into true and false cysts. The true cysts have a specific secreting membrane either epithelial, endothelial or parasitic in nature. The false cysts have a dense hyaline fibrous tissue or a layer of condensed splenic tissue. The contents of the latter may be hemorrhagic, serous, inflammatory or degenerative. Lubarsch<sup>5</sup> divides them into lymphatic cysts with clear fluid, hemorrhagic cysts with bloody contents, and dermoid cysts with sebaceous substance. Paul<sup>6</sup> classifies them into hydatid; multiple serous cysts, usually associated with polycystic disease of the kidney; and single or dermoid, epidermoid, serous or blood cysts.

A histological classification has little to offer. Some writers will classify cysts according to contents, others according to etiology, and still others depend

\* Received for publication April 2, 1947.

From the Medical Service, Queens General Hospital, Dr. James R. Reuling, Director.

on the pathology. Fowler<sup>7</sup> divided all cysts into primary and secondary, and his classification, outlined below, is that which is most often used:

Primary 21 per cent	{	Congenital—originate by infoliation and dilatation
		Traumatic
		Inflammatory
		Neoplastic—dermoid, epidermoid, lymphangioma
		Parasitic—echinococcal
Secondary 79 per cent	{	Trauma
		Degeneration
		Inflammation

#### CASE REPORT

A married female 19 years of age, was admitted to the medical service of the Queens General Hospital on May 25, 1946, with a complaint of pain in the left chest, together with malaise, anorexia, and a weight loss of 18 pounds in three months. Two weeks before admission she began to experience severe stabbing pains in the left lower antero-lateral thoracic region. At the same time she noted a diffuse tender swelling in the same area. Deep respiration, coughing, and sneezing accentuated the pain. She ran a low-grade fever and developed a slight cough at the same time. The pain radiated to the back from the epigastrium along the infracostal border and



FIG. 1. Displacement of stomach to the right of the midline.

to the left shoulder. She was placed on sulfa drugs and penicillin by her local physician, but as the swelling persisted hospitalization was advised.

The past history was essentially negative except for a normal delivery two years previously. Family history was non-contributory.

Physical examination revealed a well-developed and nourished young girl, complaining of pain in the left lower chest and avoiding all motion. Positive findings were limited to the lower thorax and abdomen. There was slight diminution of breath



FIG. 2. Displacement of stomach to right by cyst of spleen.

sounds in the left base posteriorly and a diffuse swelling presented itself anteriorly in the left upper quadrant, which seemed soft and cystic. The outlines of the spleen and liver were not palpable. Moderate tenderness was elicited over the mass, which was about half the size of a grapefruit.

Laboratory studies revealed a normal leukocyte and differential count on three occasions, with 3,400,000 red cells and 8 gm. of hemoglobin. Serologic test for syphilis, blood proteins, urea nitrogen, cephalin flocculation, and alkaline phosphatase



were all normal. Platelets numbered 92,000, and bleeding and clotting times were normal.

Fluoroscopy revealed a clear left costo-phrenic sinus but a fixed left diaphragm. A roentgenogram of the chest was normal. Gastrointestinal studies showed no intrinsic pathology but the stomach was moderately displaced to the right and to a lesser extent anteriorly by an extrinsic mass (figures 1, 2, 3). The colon studies showed no displacement. Genito-urinary films revealed a congenitally displaced left kidney

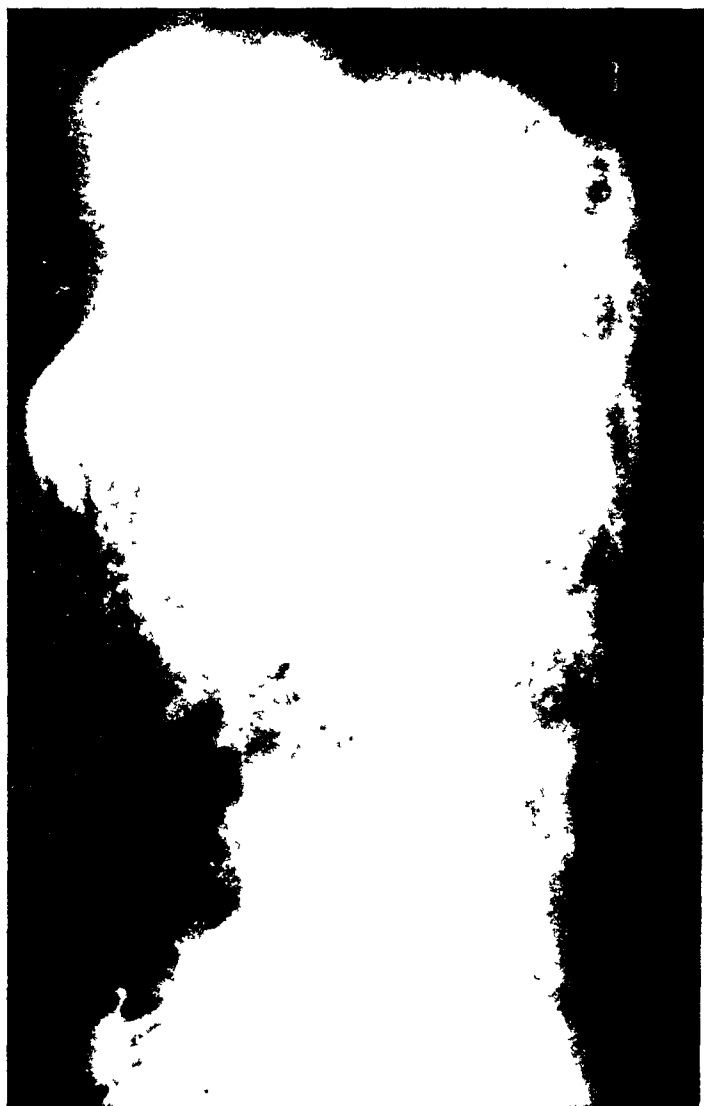


FIG. 3. Anterior displacement of stomach as seen in lateral view.

with a double pelvis lying to the right of the vertebral column. It was felt the patient had a congenital horse-shoe kidney, atopic and located on the right, which condition was probably unrelated to the splenic cyst (figure 4).

On the twenty-second hospital day the patient was taken to the operating room, where a large cystic spleen was found (figure 5). Approximately 1,000 c.c. of a brownish fluid were aspirated before removal of the viscus. The fluid was sterile and had a specific gravity of 1.028 and a leukocyte count of 59,000 cells, 85 per cent being polymorphonuclear leukocytes and 15 per cent lymphocytes.

Post-operatively the patient did well. The platelet count was followed for a week post-operatively, rising to a high of 212,000 on the seventh day.

The pathological report by Dr. A. Angrist noted the following: "Specimen consisted of a spleen weighing 610 gm. There was an incision into a loculated cyst filled with thick bloody fluid. The capsule was smooth, dark red in color and contained several hard grayish calcified zones. On section the greater part of the spleen was



FIG. 4. Displaced left kidney to the right of the vertebral column.

made up of loculated large cystic areas lined by a calcified tissue. The impression was that we were dealing with a splenic cyst with a connective tissue wall that showed fibrosis, atheromatosis and slight calcification."

#### DISCUSSION

The etiology of splenic cysts is unknown, though several independent factors are suspected. The presence of these tumors in women of childbearing age has

been commented on by DeLee,<sup>8</sup> McClure<sup>4</sup> and Denneen.<sup>9</sup> DeLee suggests that the cyclical hormone changes occurring during menstruation and pregnancy alter the size and congestion of the spleen, and that trauma during the phase of enlargement and congestion may be sufficient to induce hematoma or cystic changes. Trauma alone is considered significant in many of the reported cases. Cystic



FIG. 5. Spleen and cyst with loculated cystic areas lined by calcified tissue.

spleens are said to have resulted from blows 10 years before with eventual infarction, hemorrhage, and cyst formation. Preëxisting splenomegaly, as a result of lues and malaria, is also felt to predispose, as the organ is more likely to be injured because of its size.

Clinically the presence of symptoms referable to the left upper quadrant and

just under the left costal margin are significant. The presence of pain depends on the size of the mass. A large one may cause the patient to complain of a heavy dragging pain; a smaller one may be less disturbing. The mass usually is soft and cystic. The spleen may or may not be outlined, again depending on the size of the mass. The presence or absence of fever is another problem which offers no help. If the cyst is of the inflammatory variety a febrile reaction will obtain. The presence of a fixed left diaphragm with diminished breath sounds is characteristic. The splenic mass displaces the immediately surrounding structures, notably the left diaphragm, the stomach, and the splenic flexure and transverse colon. Pancreatic and ovarian cysts may offer a problem but they do not offer resistance to the left costal margin. Ovarian cysts may be traced into the pelvis, whereas splenic cysts enlarge, transversely. The large leukemic spleen also grows down towards the pelvis and we do not see the spreading of the ribs and the involvement of the left diaphragm. These clinical findings, if considered with the roentgen visualizations, make the diagnosis obvious.

Roentgenologically, a splenic mass growing anteriorly and under the costal margin causes visceral displacement, and elevates the left diaphragm to impair the latter's motion. The barium-filled stomach is displaced to the right, the colon is pushed down and to the right. The left kidney may also be displaced downward. Calcification occurs frequently enough in these splenic tumors to have been commented upon by Bachman,<sup>10</sup> Gallagher,<sup>11</sup> Jamison,<sup>12</sup> Shawan,<sup>13</sup> and Snoke<sup>14</sup> in their case reports. Ostro and Makover<sup>15</sup> feel that any spleen that grows downward and anteriorly will not displace the neighboring organs as will a splenic cyst. Benton<sup>16</sup> feels that downward displacement of the splenic flexure is almost pathognomonic of large cysts of the spleen.

The laboratory is of no help in the differential diagnosis except in a negative fashion.

Therapy is specific. All cases are amenable to surgery and usually do very well.

#### SUMMARY

1. A case report of a patient with a splenic cyst is given because of the relative infrequency of the condition.
2. The etiology of splenic cysts is still obscure.
3. The diagnostic features of a palpably enlarged tumor, paucity of symptoms, occasional calcification, pathognomonic roentgenological findings are stressed.

#### BIBLIOGRAPHY

1. ANDRAL, G.: *Precis d'anatomie pathologique*, Paris, 1829, ii, 432.
2. ROBERSON, F.: Solitary cysts of spleen, *Ann. Surg.*, 1940, iii, 848-850. (Pemberton J. de J., discussor of paper.)
3. SWEET, R. H.: Single true cysts of the spleen, *New England Jr. Med.*, 1943, ccxxviii, 705-710.
4. McCLURE, R. D., and ALTMEIER, W. A.: Cysts of spleen, *Ann. Surg.*, 1942, cxvi, 98-102.
5. LUBARSCH, O.: Die Zysten der Milz, *Im Handbuch der Speziellen Path., Anat. und Histol.*, J. Springer, Berlin, 1927, i, 718-728.
6. PAUL, MILROY: Cysts of spleen, *British Jr. Surg.*, 1943, xxx, 336-339.
7. FOWLER, R. H.: Cystic tumors of the spleen, *Surg., Gynec. and Obst.*, 1940, lxx, 213-223.
8. DeLEE, J. B.: *Principles and practice of obstetrics*, 1930, W. B. Saunders & Co., Philadelphia, p. 106.

9. DENNEEN, E. V.: Hemorrhagic cyst of spleen, *Ann. Surg.*, 1942, cxvi, 103-108.
10. BACHMAN, A. L.: Calcification in the splenic region, *Am. Jr. Roent.*, 1939, xli, 931-949.
11. GALLAGHER, P., and MOSSBERGER, J. I.: Calcified multilocular cysts of spleen, *Ann. Surg.*, 1942, cxvi, 933-937.
12. JAMISON, E. M., and SMITH, O. F.: Calcified cyst of spleen: report of case, *U. S. Nav. Med. Bull.*, 1945, xlv, 537-541.
13. SHAWAN, H. K.: Calcified cyst of spleen, *Ann. Surg.*, 1937, cvi, 469-474.
14. SNOKE, P. O.: A solitary calcified cyst of the spleen, *Am. Jr. Med. Sci.*, 1943, ccvi, 726-730.
15. OSTRO, S., and MAKOVER, H. B.: Non-parasitic cyst of spleen with special reference to roentgenological aid in diagnosis, *Am. Jr. Roent.*, 1937, xxxvii, 782-785.
16. BENTON, R. W.: Large cysts of the spleen, *Jr. Am. Med. Assoc.*, 1932, xcix, 1674-1676.

---

### TROPICAL EOSINOPHILIA WITH REPORT OF A CASE TREATED WITH PENICILLIN \*

By PAUL H. MORTON, M.D., F.A.C.P., Commander (MC) USNR, *Coronado, California*, and CARL C. JONES, Lieutenant (jg) (MC) USNR, *Winston-Salem, North Carolina*

SEVERAL articles and case reports have recently appeared in the literature concerning this disease which was first described in 1919,<sup>5</sup> and was given the name tropical eosinophilia by Weingarten<sup>1</sup> who in 1943 reported 81 cases. Since then all reported cases have been successfully treated with organic arsenical drugs.

The disease is characterized by lassitude, fever, anorexia, weight loss, and cough. The latter occurs characteristically in the early morning hours between 1 and 5 a.m. and is accompanied by asthmatic wheezing. Later dyspnea and orthopnea develop. A marked eosinophilia is present, sometimes reaching as high as 70 to 80 per cent, together with a leukocytosis. There is a relative as well as absolute increase in eosinophiles, all of which appear to be normal mature forms. If the disease remains untreated, it becomes chronic.

Weingarten's series of cases was observed in the coastal regions of India around Bombay. One of them fortuitously contracted syphilis and was given specific treatment with neoarsphenamine, following which his hypereosinophilia subsided to normal. As a result of this observation, Weingarten treated similar cases with the same drug, after which all apparently became well.

The only other conditions showing such a high eosinophilic count are periarthritis nodosa and eosinophilic leukemia. However, in tropical eosinophilia, immature forms of eosinophiles are not found and the course is usually benign.

In 1944, Emerson<sup>2</sup> reported a case in a young naval officer who had lived in India before the war, where he had suffered with asthma and sinusitis. He was found to have a leukocytosis with 20 per cent eosinophiles which later arose to 78 per cent following the incision and drainage of a staphylococcic liver abscess. He was successfully treated by the oral administration of carbarsone.

Parsons-Smith<sup>3</sup> in 1944 reported a case he observed in an English airman stationed in Egypt. Symptomatic treatment for asthma gave no relief. At this

\* Received for publication June 18, 1947.

time Weingarten's article arrived in the middle East, and neoarsphenamine was then employed with dramatic success.

In 1945 another case was reported by Hirst and McCann<sup>4</sup> in another naval officer serving in the Pacific area, who suddenly developed severe asthma accompanied by headaches. He had never been in India and his overseas duty had been in Central America and the central and south Pacific islands. His asthmatic symptoms had their onset two years previously in Samoa. He was found to have a leukocytosis of 15,000 cells per cu. mm. with a hypereosinophilia up to 72 per cent, which later rose to 82 per cent. The sputum was loaded with eosinophiles. No parasites could be found. His response to neoarsphenamine therapy was again dramatic, five doses four days apart resulting in prompt and complete cure.

Van der Sar and Hartz<sup>5</sup> in 1945 reported their experiences with cases of tropical eosinophilia observed in Curaçao, and conclude that they have demonstrated the relationship between this disease and filariasis since they were able to demonstrate microfilariae in a biopsied lymph node from a typical case of tropical eosinophilia.

Apley and Grant<sup>6</sup> in 1945 reported on five cases observed in England in servicemen invalided back from the Middle East, all of whom promptly responded to arsenical therapy. They further discussed the possible relationship between Loeffler's syndrome, tropical eosinophilia, periarteritis nodosa, and bronchial asthma, which they classify together under the term "E P syndrome," meaning eosinophilia with pulmonary infiltration.

In 1946 Irwin<sup>7</sup> reported two additional cases of tropical eosinophilia originating in the southwest Pacific which also responded to arsenical therapy. He calls attention to the possibility of this being caused by filariasis, as suggested by Van der Sar and Hartz, inasmuch as both of his patients had spent considerable time in an area where *Wuchereria bancrofti* is prevalent. However, repeated examinations of the blood at all hours revealed no microfilaria and the biopsies from muscle, lymph node, and bone marrow showed no filariae although both patients had positive skin test reactions to *Dirofilaria immitis* antigen. He pointed out, however, that false positives are common in the use of this antigen.

It has thus been established that arsenical compounds are specific in the treatment of tropical eosinophilia and that prompt and complete recovery follows their use. As far as we can determine it has never been effective in the other conditions characterized by marked eosinophilia. The effect of penicillin in tropical eosinophilia has not to our knowledge been reported previously. It is for this reason that we decided to test its action in this disease.

#### CASE REPORT

The patient, a 23 year old Marine sergeant, was admitted to a naval hospital on February 11, 1947, complaining of nocturnal cough, progressive loss of weight amounting to 28 pounds during the past six months, and general malaise. He stated that he had been perfectly well and healthy until after his return from the western Pacific (Japan) in March, 1946. One month later he noted the onset of a deep nocturnal cough productive of a moderate amount of thick, tenacious, dark-colored sputum. Although the cough was present to some extent during the day it usually became worse after going to bed and would awaken him around 2 a.m. He would usually vomit after a particularly severe coughing spell, often being unable to retain his break-

fast. He had never coughed up any parasites and denied hemoptysis. His symptoms gradually became worse so that by November, 1946 he wheezed audibly on respiration and noticed dyspnea for the first time. Often he was unable to remain lying down due to the dyspnea, which became progressively worse. At the time of his return from overseas he weighed 170 pounds, as compared with 140 pounds at the time of his hospital admission. He had not been aware of any fever, night sweats, diarrhea, or genito-urinary symptoms suggestive of filariasis, or other parasite infestations.

During childhood he had contracted the usual diseases. Tonsils and adenoids were removed at the age of six years. He denied past allergic symptoms. During the war he had served on the islands of Guadalcanal (where he contracted malaria in 1942), Tulagi, Samoa, Tinian, Saipan, and Japan. He had spent a total of four years overseas in the Pacific area. His mother, father, sister, brother, and wife were all in good health, and there was no family history of allergy, tuberculosis, cancer or other familial diseases.

Physical examination upon admission to the hospital revealed a pale, asthenic, thin, 23 year old white male, appearing chronically ill. Temperature, pulse, and respiratory rate were normal. His height was 65 inches and he weighed 140 pounds. He coughed frequently. The facial skin showed pitted scars of former acne vulgaris. The body skin was rough and granular. The subcutaneous tissues were normal. The tonsils were surgically absent. The posterior cervical lymph nodes were small, discrete, firm and non-tender. This was also true of the submaxillary, right axillary, inguinal, saphenous and epitrochlear nodes. In the left axilla there were several large discrete, non-tender lymph nodes, each the size of a walnut. The trachea was in the midline, the chest symmetrical and fixed in a position of moderate inspiration. Upon auscultation, asthmatic rhonchi, sibilant and sonorous, were heard mainly during expiration. The chest was hyper-resonant, and tactile and vocal fremitus were normal. The heart rate was 88 per minute with a regular sinus rhythm. No thrills or murmurs were present and the heart was not enlarged. The abdomen was scaphoid, non-tender, and no masses were felt. The spleen was not palpable. The genitalia were normal adult male, and the extremities appeared normal. Chest roentgen-ray revealed moderate accentuation of both hilar and peribronchial markings but no parenchymal lesions. This was considered to be consistent with chronic bronchitis or bronchial asthma. Blood studies revealed 5,530,000 erythrocytes per cu. mm. with 15 gm. hemoglobin (107 per cent) and a leukocytosis of 28,950, 57 per cent of which were eosinophiles, with 15 per cent mature neutrophils, 3 per cent monocytes, and 22 per cent lymphocytes. The eosinophiles were somewhat larger than those usually seen, with 2 per cent band forms and 98 per cent mature segmented forms. Examinations of stained sputum smears revealed numerous eosinophiles with a few neutrophils, many Curschman's spirals, some elastic fibers and an apparently normal bacterial flora. No fungi, molds, or parasites were ever found in the sputum in spite of repeated examinations, and stained smears for acid-fast bacilli were invariably negative. Urinalyses were normal and the erythrocyte sedimentation rate (Westergren) was 6 mm. per 60 minutes. All stool specimens including those collected for 24 hours after purgation with magnesium sulfate were invariably negative for all ova and parasites. The Kahn test was negative.

During hospitalization the patient was free of dyspnea unless he lay down or exercised. After going to bed at night he noted the progression of wheezing, dyspnea and cough, particularly in the early morning hours. The cough was severe and productive of tenacious dark sputum, and paroxysms were usually followed by vomiting, so that he usually lost his breakfast. His symptoms were controlled with adrenalin and benadryl. However, his breathing during sleep was labored and audible throughout the ward. Roentgen-rays of the paranasal sinuses revealed some haziness of the frontal and maxillary sinuses bilaterally. Repeated chest roentgen-rays showed no change from the films made following admission. During the first week of hospitali-

zation he lost six additional pounds of weight. Temperature, pulse, and respiration remained normal. The white cell count increased to 17,750 with 61 per cent eosinophiles. An electrocardiogram made on February 17 revealed no evidence of myocardial damage, with normal sinus rhythm, rate 75 per minute, P-R interval 0.18 second, and T waves upright in all leads. The Davidsohn test was negative as were all routine febrile agglutination tests. Dark-field examinations of the blood serum were negative for parasites. Stool cultures were negative and sputum cultures on Sabouraud's medium showed no growth. The erythrocyte sedimentation rate was now 13 mm. in 60 minutes. On February 22 a large lymph node 25 mm. in diameter was removed from the left axilla. Upon microscopic examination, the lymph node architecture was well preserved. The capsule was thin and showed some blood vessel congestion. The follicles showed marked hyperplasia of the germinal centers with much lymphoblastic activity. The mature lymphocytes about the follicles were lined up in almost concentric rings. The peripheral sinuses were dilated and in some areas contained lymphocytes. Reticulo-histiocytic elements showed moderate hyperplasia, and an occasional large macrophage containing brown pigment granules could be seen. Large numbers of plasma cells and polys were present. No evidence of malignancy was noted and the histologic appearance of the node was consistent with the picture seen in tropical eosinophilia. Pathologically the histological diagnosis was chronic lymphadenitis with reticulo-endotheliosis.

The following skin tests were employed: (1) *Dipilidium caninum*, 0.5 c.c., intradermally, was positive, showing erythema, pseudopodia, and enlargement of the wheal to one-half inch within 15 minutes. The control remained negative. (2) *Trichinella spiralis*, 1:10,000, 0.02 c.c., intradermally was negative. (3) Coccidioidin, intradermally, gave positive results. (4) *Dirofilaria immitis*, 1:10,000, produced an immediate positive reaction in 30 minutes, the control remaining negative. (5) P.P.D. tuberculin test (first strength) was negative. (6) Skin tests for 36 common allergens, including air-borne pollens, foods, and animal dander were all negative.

On February 22 the erythrocyte sedimentation rate was 13 mm. in 60 minutes, hemoglobin 14.5 gm. (103 per cent), leukocytes 17,450, 49 per cent of which were eosinophiles. The platelet count was 378,000. Chest roentgenograms revealed some clearing of the hilar markings as compared with previous films. Roentgen-rays of the skull, long bones, and muscles were reported as negative for soft tissue calcifications which might represent encysted parasites. The patient now weighed 132 pounds. The basal metabolic rate was plus 13 per cent. The patient was treated with intramuscular adrenalin-in-oil and oral benadryl which gave some relief of his severe asthmatic symptoms. After seven days of this treatment a concurrent decrease in symptoms, leukocytosis and eosinophiles to 30 per cent occurred. This was probably coincidental.

Commencing on March 4, 100,000 Oxford units of penicillin were given intramuscularly every three hours to a total of 8,000,000 units. By the end of the course of penicillin, the eosinophilic count had increased slightly. The patient continued to gain weight and was free of symptoms. No changes were seen in the lung fields by weekly roentgen-rays.

Following the cessation of penicillin therapy, two weeks were allowed to elapse, but no significant change in the blood picture occurred, the leukocyte count remaining about the same and the eosinophiles ranging between 20 per cent and 30 per cent. Finally, on March 22 a course of six injections of neoarsphenamine intravenously was commenced. At first there was a steady decline in the eosinophilia from 30 per cent to 11 per cent, then it temporarily rose as high as 17 per cent, finally subsiding to within normal limits. The case could not be followed further, as the patient was discharged from the Service and returned to his home. When last seen in mid-April, he was gaining weight, symptom-free, and his blood counts were still normal.



*Differential Diagnosis:* The fact that this patient had served in the Pacific area throughout the war, including 11 months in Samoa where the *Wuchereria bancrofti* abounds, probably accounts for his illness which, however, did not become manifest until after he returned to the United States. The positive reaction to *Dirofilaria immitis* antigen, obtained through the courtesy of Dr. H. W. Brown of the Columbia University School of Public Health, is probably of significance as evidence of filariasis, although it is known that approximately 10 per cent false positives occur.<sup>8</sup> This antigen which is an extract of the dog heart-worm has not, according to Huntington,<sup>9</sup> proved to be strictly specific for the filaria group since unmistakable cross-reactions with ascaris sometimes occur. Huntington further states that its value as a diagnostic aid in individual cases is decidedly limited.

No ova or parasites were ever found in the blood, urine, feces, lymph node biopsy, or sputum, although each was examined repeatedly. Those particularly sought for were *Strongyloides stercoralis*, *Schistosoma mansoni*, *Necator americanus*, *Ascaris lumbricoides*, and *Entameba histolytica*.

All agglutination tests were negative, including those for heterophile antibodies, brucellosis, typhoid-paratyphoid, tularemia, and typhus. A diagnosis of trichinosis was considered unlikely, although muscle biopsy was declined. The sputum was cultured for yeasts and fungi with negative results.

Loeffler's syndrome<sup>10, 11, 12, 13</sup> was considered. This disease is characterized by transitory pulmonary infiltrations, relatively high eosinophilia in blood and sputum and relatively mild, usually afebrile, clinical course. According to a recent editorial in the Journal of the American Medical Association<sup>14</sup> much remains to be learned about these transitory infiltrations in the lungs. The chest roentgen-ray findings in this case were not consistent with a diagnosis of Loeffler's syndrome. Periarteritis nodosa and intrinsic bronchial asthma were also considered, as well as eosinophilic leukemia and Hodgkin's disease. Finally, the therapeutic test gave convincing evidence that this was tropical eosinophilia as described by Weingarten.<sup>1</sup>

## DISCUSSION

Apley and Grant<sup>6</sup> in their excellent treatise pointed out the similarities between intrinsic asthma, periarteritis nodosa, Loeffler's syndrome, and tropical eosinophilia. These four diseases have many common features, including a chronic course, hypereosinophilia, asthmatic symptoms and signs, and no obvious etiology. They suggest that the difference between tropical eosinophilia and Loeffler's syndrome is more apparent than real, and that it would be profitable to consider them merely as different manifestations of the same disease process. They further suggest that this group of diseases be referred to as the "E-P" syndrome, meaning "eosinophilia with pulmonary disease."

That tropical eosinophilia can be cured by arsenicals leaves one to speculate concerning its etiology. The consensus is that it is an allergic response to a variety of allergens, including infestation with animal parasites such as mites, amebae, or filaria. However, an infestation with these parasites does not invariably produce the syndrome.

As has been shown repeatedly, the effect of arsenic in producing a complete recovery in tropical eosinophilia is remarkable but as far as we were able to determine, arsenicals have not been tried in the other three conditions, and penicil-

lin, in none of them. For this reason, we administered penicillin to this case, and as far as we could determine it had absolutely no effect.

The weight of evidence in regard to this group of diseases will doubtlessly continue to be that they are of an allergic nature. Rich<sup>15, 16</sup> has advanced the hypothesis that the lesions of periarteritis nodosa are the result of hypersensitivity, and in 1942 he reported five autopsies on patients who had serum sickness before death. In all of them he was able to demonstrate the characteristic lesions of periarteritis nodosa. He later demonstrated similar vascular lesions in two patients following reactions to sulfonamide therapy, and in the following year Rich and Gregory<sup>17</sup> succeeded in producing similar lesions experimentally in rabbits by sensitizing them to horse serum. This appears to be additional evidence in support of Apley and Grant's classification of these four diseases under the "E-P syndrome."

In regard to filariasis being a factor, whether allergic or infective, in tropical eosinophilia, it is known that after patients are removed from endemic areas they become symptom-free because the filaria are unable to multiply until they undergo further passage in mosquitoes, and hence die out. However, reliable therapeutic agents against filariasis are not known. The diagnosis is usually made without demonstrating the filaria and laboratory tests are seldom helpful.<sup>18</sup>

It is our opinion, unsupported by concrete evidence, but nevertheless in accordance with the conclusions of Van der Sar and Hartz, that this patient acquired a minimal infestation with *Wuchereria bancrofti* during his stay in Samoa. Following the death of the parasites upon his return to a temperate climate he developed the typical signs and symptoms of tropical eosinophilia. This failed to respond to treatment with penicillin but promptly subsided following the administration of neoarsphenamine.

#### SUMMARY

A case is presented in which the clinical history, course and laboratory findings were consistent with a diagnosis of tropical eosinophilia.

The patient had been stationed in Samoa and gave a positive skin reaction to *Dirofilaria immitis*. This appears to be additive evidence to support the hypothesis of Van der Sar et al. and others, that tropical eosinophilia may be due to filarial infestation.

Penicillin is of no therapeutic value in this disease although the empirical use of organic arsenicals is amazingly effective.

#### BIBLIOGRAPHY

1. WEINGARTEN, R. J.: Tropical eosinophilia, *Lancet*, 1943, i, 103-105.
2. EMERSON, KENDALL: Tropical eosinophilia, *U. S. Nav. Med. Bull.*, 1944, xlii, 118-123.
3. PARSONS-SMITH, B. G.: Tropical eosinophilia, *Lancet*, 1944, i, 433-434.
4. HIRST, W. R., and McCANN, W. J.: Tropical eosinophilia, *U. S. Nav. Med. Bull.*, 1945, xliv, 1277-1281.
5. VAN DER SAR, A., and HARTZ, H.: The syndrome, tropical eosinophilia, and microfilaria, *Am. Jr. Trop. Med.*, 1945, xxv, 83-96.
6. APLEY, J., and GRANT, G. H.: Tropical eosinophilia, *Lancet*, 1945, i, 812-813.
7. IRWIN, J. W.: Tropical eosinophilia, *Ann. Int. Med.*, 1946, xxv, 329-339.
8. BROWN, H. W.: Personal communication.
9. HUNTINGTON, R. W., JR.: Skin reactions to *Dirofilaria immitis* extract, *U. S. Nav. Med. Bull.*, 1945, xliv, 707-717.

10. LÖFFLER, W.: Zur Differential-Diagnose der Lungeninfiltrierungen; über flüchtige Succedan-Infiltrate (mit Eosinophilie), Beitr. z. Klin. Tuberk., 1932, lxxix, 368. Die flüchtigen Lungeninfiltrate mit Eosinophile, Schweiz. med. Wchnschr., 1936, lxvi, 1069.
11. JONES, S. H., and CARLETON, R. S.: Eosinophilic infiltration of the lungs (Loeffler's syndrome), New England Jr. Med., 1944, ccxxxix, 356-358.
12. HANSEN-PRUSS, O. C., and GOODMAN, E. G.: Allergic pulmonary consolidations, Ann. Allergy, 1944, ii, 85-108.
13. BAGENSTOSS, A. H., BAYLEY, E. C., and LINDBERG, D. O. N.: Loeffler's syndrome: report of a case with pathologic examination of the lung, Proc. Staff Meet., Mayo Clinic, 1946, xxi, 257-265.
14. Current Comment: The allergic pulmonary reactions of Loeffler's syndrome, Jr. Am. Med. Assoc., 1947, cxxxiii, 325.
15. RICH, A. R.: Rôle of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulfonamide therapy, Bull. Johns Hopkins Hosp., 1942, lxxi, 123-140.
16. RICH, A. R.: Additional evidence of rôle of hypersensitivity in etiology of periarteritis nodosa: another case associated with sulfonamide reaction, Bull. Johns Hopkins Hosp., 1942, lxxi, 375-379.
17. RICH, A. R., and GREGORY, J. E.: Experimental demonstration that periarteritis nodosa is manifestation of hypersensitivity, Bull. Johns Hopkins Hosp., 1943, lxxii, 65-88.
18. HODGES, L. G., DENHOFF, E., and VANDERVEER, J. B.: Early filariasis (Bancrofti) in American soldiers, Am. Jr. Med. Sci., 1945, ccx, 207-222.

---

## SULFADIAZINE NEPHROSIS WITH HYPERCHLOREMIA AND ENCEPHALOPATHY \*

By WALTER T. GOODALE, M.D., *Boston, Massachusetts*, and THOMAS D.  
KINNEY, M.D., *Cleveland, Ohio*

LUETSCHER and Blackman have described a peculiar syndrome of hyperchloremia and encephalopathy, occurring in toxic nephrosis following sulfathiazole therapy.<sup>1</sup> The patients initially showed the usual critical oliguria or anuria, with azotemia, acidosis and a normal or low serum chloride level, which are typical of most acute toxic nephroses. The diuresis which followed this initial stage, however, was not the usual diuresis which is commonly welcomed as an indication that the patient will probably recover. On the contrary, despite a subsiding azotemia and acidosis, diuresis in these cases was accompanied by a striking elevation of the serum sodium and chloride levels. As this hypertonicity of the serum and body fluids increased, signs of dehydration and a severe encephalopathy appeared. The hyperchloremic encephalopathy may have been the major cause of death in at least two of the five cases reported, rather than the uremia or any other complication. In two cases treated with 3 to 5 liters of salt-free intravenous fluids daily, the serum chloride returned promptly to a normal level and the uremia continued to improve. The encephalopathy persisted, however, subsiding gradually over many months in one patient, but proving eventually fatal in the other case long after the uremia and hyperchloremia were controlled.

\* Received for publication January 18, 1949.

From the Departments of Medicine and Pathology of the Peter Bent Brigham Hospital and the Harvard Medical School.

The primary renal defect responsible for hyperchloremia was clearly shown to be an inadequate tubular reabsorption of water in the face of continued electrolyte retention.<sup>1</sup> The serum bicarbonate level was not depressed, unlike the hyperchloremia found after administration of calcium chloride or other acid-producing salts.<sup>2</sup> Despite serum chloride levels of 140 to 160 milliequivalents per liter (normal 100 to 110), the urine, though always of considerable volume in the hyperchloremic stage, showed a very low fixed chloride concentration. Similarly, in one patient it was shown that 97 per cent of the chloride in the glomerular filtrate was reabsorbed by the tubules, while only 90 per cent of the water was reabsorbed. Glomerular filtration was 30 per cent of the expected normal rate.

Autopsied cases showed a severe toxic tubular nephrosis with necrosis and thrombosis of adjacent interlobular veins and minimal glomerular damage. The brains examined showed widely scattered foci of gliosis, edema and hemorrhage.

The extreme degree of hyperchloremia without acidosis was considered to be clinically almost unique among renal disease and among other causes of electrolyte disturbance. A comparable hyperchloremia, however, has been produced experimentally in dogs by Winkler and his co-workers.<sup>3, 4</sup> By injecting hypertonic saline solution they produced chloride levels up to 193 milliequivalents per liter and found a generalized intracellular dehydration as well as a loss in intracellular potassium. The cerebral type of death in these dogs, without cardiorenal failure, was somewhat reminiscent of Luetscher's cases of hyperchloremia in man. There was no evidence for the existence of a critical level of either sodium or chloride in dogs.

Even since the original report of hyperchloremia in sulfathiazole nephrosis, the syndrome has not been widely recognized or reported.\* It therefore seemed worthwhile to report a case which followed the oral administration of small doses of sulfadiazine.

#### CASE REPORT

A 23 year old single unemployed Italian man entered the Peter Bent Brigham Hospital on Dec. 14, 1945, in coma.

At the age of seven he developed chronic osteomyelitis of the right femur, treated by open drainage, with fractures of the same bone and recurrence of the infection at 10 and 13 years of age. At 10 years of age he also had pyelitis. Up to the age of 17, he was crippled by an increasing shortening and bowing of this leg, requiring a lift and brace. At the age of 17, six years before the present illness, he had had a supracondylar osteotomy at the Massachusetts General Hospital to correct the deformity. Sulfanilamide was given prophylactically, 3 to 6 gm. daily for six days. Nine days postoperatively a staphylococcus infection recurred at the operative site requiring two courses of seven days each of sulfanilamide, 5 to 6 gm. daily, and three days of sulapyridine, 4 gm. daily. Urine, white blood count and hemoglobin remained normal throughout the three month hospital course without drug fever or rash.

Recovery followed without further recurrence and he was left with only a slight limp from a one inch shortening. As a devotee of boxing and a professional sparring partner, he received frequent blows to the head but no known concussion. He was considered by his family physician to be an inadequate person, never able to hold a

\* Maisel, Kubik and Ayer<sup>5</sup> reported a case of encephalopathy following sulfathiazole therapy with an elevated non-protein nitrogen which fell to normal terminally, without progressive oliguria, and yet with a progressively fatal coma. At autopsy, both renal and cerebral lesions were found, quite similar to those reported by Luetscher and Blackman. Clinically and pathologically the resemblance was close enough to suggest that the hyperchloremic syndrome may have been present, although no serum chloride determination was reported.

steady job, blaming his incapacities on his former deformity, occasionally showing extremely introspective as well as paranoid behavior. He would often threaten people unaccountably, occasionally quite violently, and in the few months preceding admission he became increasingly nervous and moody.

Three weeks before admission he developed malaise, low back pain and after several days a headache, chilly sensations and a fever up to 103 degrees. The urine showed no albumin or sugar; the sediment was not examined. Physical examination was negative. He was given 1 gm. of sulfadiazine and 2 gm. of sodium bicarbonate orally every three hours for a total of only four doses. On the second day his temperature was normal and he was up and about the house. On the third day he complained of a headache and suddenly became very moody, finally quite violently paranoid, threatening his family with a carving knife for no apparent reason and attempting to strangle a neighbor.

He was accordingly first admitted to the Boston Psychopathic Hospital where he was found to be combative, confused, acutely maniacal, and so violent that he had to be kept in padded isolation. Physical examination was essentially negative. For the first seven days in the Psychopathic Hospital observations were necessarily limited by his extreme violence. His appetite and fluid intake were fair. Urination was noted to be very scanty, but it was uncontrolled and not measured. On the first day lumbar puncture under pentothal anesthesia showed normal dynamics, 15 lymphocytes per cubic millimeter, a positive Pandy test, and a total protein of 25 mg. per cent; lumbar puncture repeated six days later showed a total protein of 95 mg. per cent. On the sixth day the blood serum non-protein nitrogen was 94 mg. per cent, rising to 200 by the twelfth day. Initial urine specimen on the twelfth day showed occasional red and white blood cells, granular casts and a 1 + albumin.

By the second week of his Psychopathic Hospital stay, he had become less violent and fairly coöperative, taking fluids well and urinating copiously, although still incontinent. From the tenth to the thirteenth day, however, he became increasingly stuporous and his total output had meanwhile risen to over 1,000 c.c. On the eleventh and twelfth days 4,000 c.c. of parenteral fluids, containing a total of only 9 gm. of sodium chloride and 3 gm. of sodium bicarbonate, were given daily and the urine output rose to almost 2,000 c.c. On the thirteenth day the non-protein nitrogen had fallen to 171 mg. per cent but the serum chloride was found to be elevated to 146 milliequivalents per liter. He was now comatose and totally incontinent.

It was decided on consultation to transfer the patient to the Peter Bent Brigham Hospital. On admission to this hospital, the rectal temperature was 101.2°, the pulse 98 and the respirations 20. The patient was a well developed, slightly obese young man who was comatose except for occasional mumbling and singing to himself. The skin was hot and dry without detectable edema. The subcutaneous tissue and muscles were firm, without signs of wasting or weight loss. A diffuse, thinly scattered, fine maculopapular rash covered the chest and back, with several small macules over the face. The right leg showed the old osteotomy scar and was one inch shorter and definitely smaller than the left. The right knee was limited to 70 degrees of flexion. The conjunctivae were suffused. The pupils were dilated and reacted slowly to light. The fundi were normal. The nasal mucosa was congested and there was a yellow mucoid exudate obstructing the nares. The breath was foul and uriniferous. The lips and tongue were extremely dry and crusted. The neck was not stiff. The chest was repeatedly clear to percussion and auscultation. The heart was not enlarged and showed a normal sinus rhythm with no murmurs or friction rubs. The abdomen, genitalia and rectum were normal. The deep tendon reflexes were hypoactive but present throughout and there was no Babinski sign.

*Laboratory Data:* Hinton negative. Urine: pH 5.5, specific gravity 1.008, albumin 2 + with occasional red cells, 1 to 3 white cells and 1 to 3 granular casts per

high power field in the unspun sediment. Urine guaiac positive, stool guaiac negative. Hematocrit 51.5 per cent, hemoglobin 17.2 gm. per cent, corrected sedimentation rate 0.9 mm. per minute, white blood cell count 6,700 with 66 per cent polymorphonuclears, 14 per cent band forms, 16 per cent lymphocytes and 4 per cent eosinophiles. Blood urea nitrogen 104 mg. per cent, serum non-protein nitrogen 170 mg. per cent, total protein 8.4 mg. per cent, fasting blood sugar 65 mg. per cent, serum carbon dioxide combining power 22 millimoles per liter, serum chloride 140 milliequivalents per liter, icteric index 15, sulfadiazine level 0. Electrocardiograms and skull films were normal. A chest film was normal except for prominence of the left ventricle. Two blood cultures and a urine culture were negative.

*Hospital Course:* An intake of over 4,000 c.c. of salt-free intravenous glucose lowered the chloride level from 140 to 113 milliequivalents per liter and the hematocrit from 51.5 to 43 per cent within the first 36 hours. The high fluid intake was continued, however, for an additional 12 hours until the report on the rapid fall in serum chloride had been received and evaluated. By 48 hours after admission the patient had received a total of 7,000 c.c. of salt-free fluids, dehydration had disappeared, a gain in weight of 3 kg. was noted, and he looked slightly edematous. Fluid therapy was therefore suspended. A few hours later his temperature suddenly rose to 105 degrees, the pulse to 144 and the respirations to 60, and the latter were deep as well as rapid. Emergency chemical determinations showed a rise in the blood urea nitrogen to 140 mg. per cent and a fall in the serum carbon dioxide combining power to 18.9 millimoles per liter. He was given 80 c.c. of a one molar sodium lactate solution and 20 gm. of salt-free albumin in 1,000 c.c. of dextrose and water. The temperature then promptly fell to 101.6°, the pulse to 100, the respirations to 40, and the serum carbon dioxide combining power rose to 21.9 millimoles per liter within a few hours. On the third day oliguria progressed gradually to a state of anuria so that intravenous fluid therapy was again suspended. Generalized edema was now obvious with pitting in the sacral region. Finally, the blood pressure fell below 100 mm. of mercury and the respirations became very shallow while the temperature rose again to 105°. There were no signs of pulmonary edema at any time, however, and an electrocardiogram and repeated examinations of the heart at this point were normal. Despite 4 units of plasma and the usual stimulants, he died 78 hours after admission, in shock, with a terminal hyperpyrexia of 108.2 degrees.

*Autopsy:* The body was that of a normally developed and well nourished white man. There was a moderate degree of pitting of the lower extremities and sacral region. The heart was not remarkable. In the lungs, large irregular areas of consolidation, proved by microscopic examination to be confluent bronchopneumonia, were found scattered throughout all the lobes. The liver appeared normal. The right kidney weighed 260 gm. and the left kidney 350 gm. They were of the usual shape. The arrangement of the ureters and renal vessels at the pelvis was normal. The renal capsules were thin and could be stripped with ease leaving smooth, firm, pale reddish-brown surfaces. Vertical sections of each kidney showed the cortex and medulla to be clearly demarcated. The cortex of each kidney measured from 1.0 to 1.2 cm. in width. The tubular striations of the papillae were clearly seen. The cut surfaces appeared edematous and moist and the cortex protruded above the capsule. The calyces and pelves and ureters were normal in shape and thickness. Numerous pinpoint hemorrhages were found in the pelvis and papillae. No significant gross findings were noted in any of the other organs. Permission for examination of the brain was not granted.

*Microscopic Studies:* Sections of kidney were fixed in Zenker's fluid and in 10 per cent formalin and stained with eosin-methylene blue, hematoxylin-eosin, Kossa's silver stain for calcium, Turnbull's blue stain for iron, and benzidine stains. The most striking renal lesions involved the tubules. Many tubules were dilated and the

lining epithelium was flattened. In others the epithelium was thin, atrophic and fragmented. Many epithelial cells were separated from the basement membranes. Other tubular areas showed definite evidence of repair with binucleated cells and mitotic figures. Three types of casts were found in the tubules (figure 1). The most prominent were large, irregular refractile masses which stained a deep blue-black with the eosin-methylene blue stain. The appearance of the material suggested calcium.

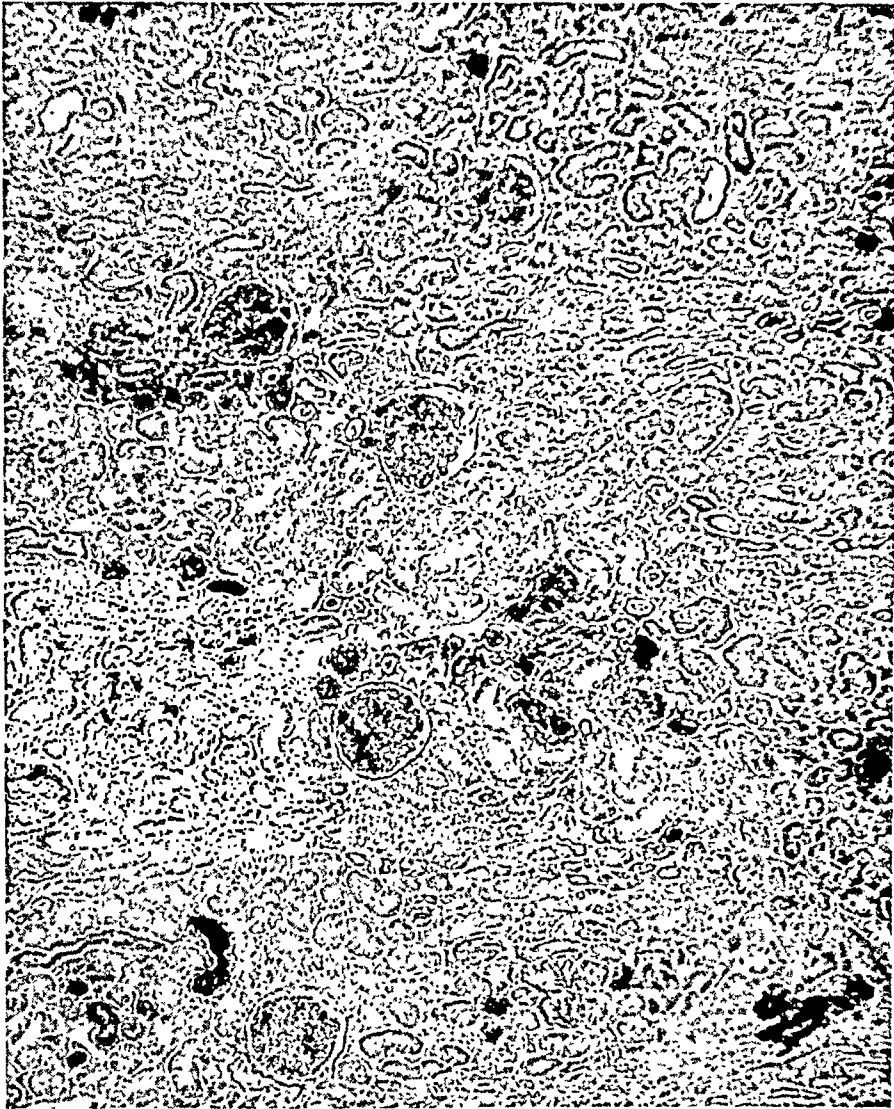


FIG. 1. Low power photomicrograph illustrating the large numbers of casts present in the tubules. Eosin-methylene blue stain.

These casts completely filled the lumina of the tubules. The lining epithelium was always disrupted to a greater or lesser degree and the epithelial cells were either swollen or fragmented (figure 2). This material did not give positive reactions to either the iron or benzidine stains. This was true as well for Kossa's silver stain for calcium phosphate. However, when sections of kidney tissue were subjected to micro-incineration these casts reacted positively to tests for calcium and to a lesser

degree for iron. These casts were present for the most part in the intercalated segments of the distal convoluted tubules, but were occasionally found in the loops of Henle and in the proximal portion of the collecting tubules. The next type of cast in order of frequency was a pale, slightly basophilic, homogeneous cast and these casts were interpreted as being made up of protein. These casts did not react with the iron, benzidine or Kossa's silver stain for calcium. The third type of cast was

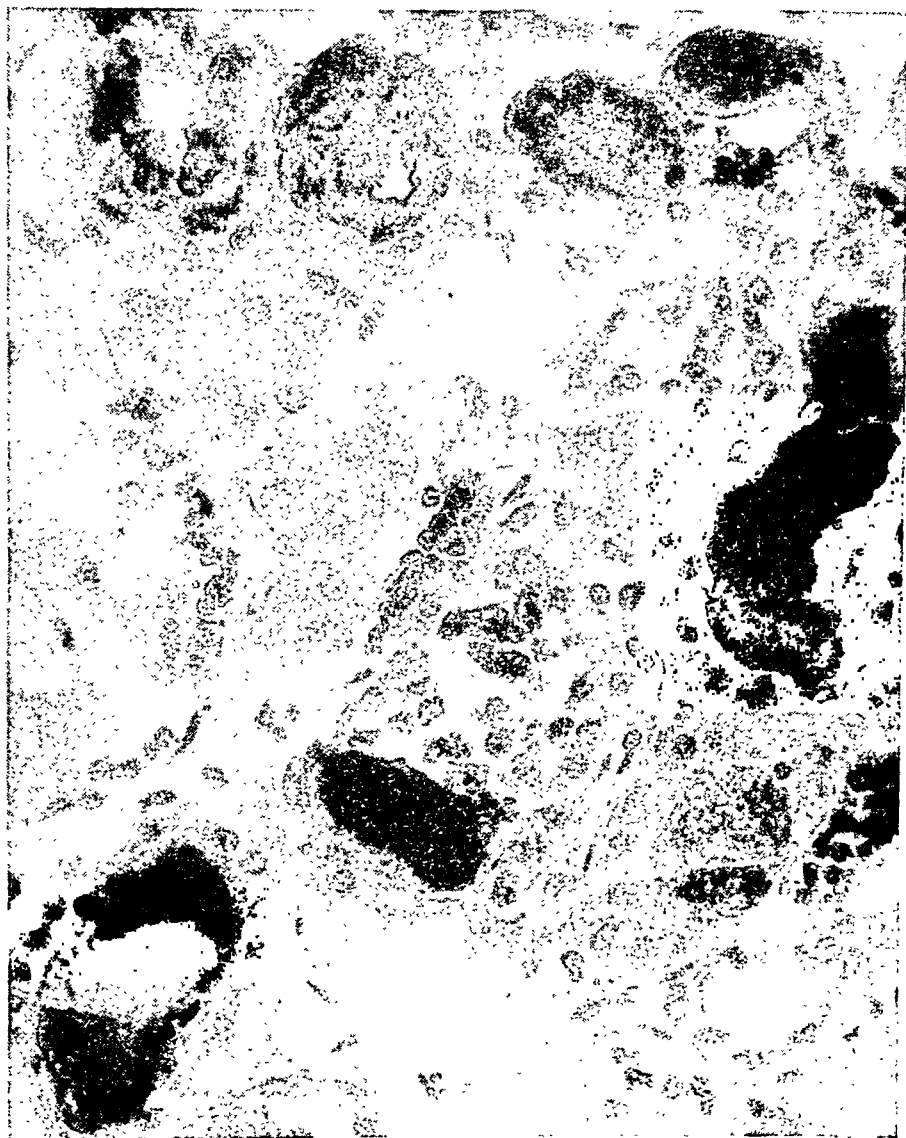


FIG. 2. High power photomicrograph showing the character of the refractile tubular casts. Eosin-methylene blue stain.

made up of finely granular material which stained reddish-brown with the eosin-methylene blue stain. This material had the appearance of hemosiderin and this was confirmed by the iron stains.

It should be noted that in addition to the above findings small collections of reddish-brown pigment suggesting hemosiderin and giving a positive reaction to the iron stains were found in the epithelium of some of the tubules.



The glomeruli were not unusual in any way. The large and small blood vessels were negative.

*Bacteriology:* *Staphylococcus aureus* was cultured from the lungs; *B. coli*, enterococci, and a rare *Staphylococcus aureus* were cultured from the right kidney pelvis; and *B. coli* from the pelvis of the left kidney.

## DISCUSSION

The clinical course and pathological findings in the case presented compare closely with those reported by Luetscher and Blackman<sup>1</sup> and serve mainly to establish the existence of the hyperchloremic syndrome following sulfadiazine, as well as following sulfathiazole as originally reported. The initial oliguria, followed by hyperchloremia, dehydration and coma appearing in the face of a diuresis, and the hyperpnea without acidosis were all similar to their findings. Clinically, however, it is impossible to say how much of the patient's encephalopathy was due to hyperchloremia, to uremia or to direct sulfonamide toxicity.<sup>5-9</sup> In addition, the patient's known background of paranoid and schizoid tendencies may have influenced the initial symptomatology which prompted his admission to a psychopathic hospital, for it is well known that organic disease, including both uremia and sulfonamide intoxication,<sup>9, 10</sup> may bring out a latent psychosis.

The extensive tubular damage, the type of casts found in the tubules and the minimal evidence of glomerular damage were similar to the renal lesions originally reported. On the other hand, thrombosis and necrosis of the interlobular veins were not found in this case, nor was there any evidence of vascular damage either in the kidneys or elsewhere in the body. The tubular lesions were more diffuse than in the cases of Luetscher and Blackman. The peculiar association of excessive tubular loss of water with continued electrolyte retention was felt by these authors to be due to a specifically localized tubular lesion. Actually, however, the lesions described in their cases were also fairly well scattered throughout the tubular system.

*Therapy:* Salt-free intravenous fluids, using up to 4 to 5 liters daily, were used by Luetscher and Blackman specifically to offset the excessive tubular loss of water and thus to lower the serum sodium and chloride to isotonic levels. Salt, or sodium in any form, is obviously strictly contraindicated in hyperchloremia. The apparently irreversible nature of hyperchloremic encephalopathy<sup>1</sup> suggests that such treatment must be prompt and vigorous, preferably started following discovery of an elevated serum chloride and before cerebral damage from hyperchloremia becomes obvious clinically. However, pulmonary edema may be a limiting factor in the intravenous administration of even small amounts of salt-free fluids, as was found in two of Luetscher's cases, and in such a situation attempts should be made to use the less effective subcutaneous or oral route of administration.

Generalized edema may also occur following the excessive use of even salt-free fluids as illustrated by the present case. The serum chloride level was lowered rapidly, and the parallel fall in hematocrit suggests that therapy produced a simple dilution of the blood and probably the remainder of the body fluids as well. The high fluid intake was mistakenly continued, however, for at least 12 hours after relief of the hyperchloremia. Meanwhile, the urine output was again falling possibly representing a change in the functional state of the kidneys as they

approached a terminal stage of the disease. With increasing oliguria, excessive fluids given once dehydration had been corrected could only have tended to form edema fluid. Generalized edema appeared in this case despite the fact that fluids administered contained no salt and despite the probability that the total body electrolyte content was never increased.\* This edema, by including the kidney as found at autopsy, may have contributed to the eventual total renal failure. In the brain, edema may have aggravated the encephalopathy as suggested by the terminal hyperpyrexia of 108.2°.

A high salt-free fluid intake is therefore probably indicated only while hyperchloremia is actually present. Once hyperchloremic dehydration is controlled the fluid intake should depend upon the urine output. It has been repeatedly emphasized that in the usual toxic nephrosis without hyperchloremia, a high fluid intake will not force an oliguric or anuric kidney to increase its urine output and will only tend to add the further complication of pulmonary or generalized edema.<sup>12, 13</sup>

Finally, generalized depletion of intracellular potassium may well be an important pathophysiological factor in these cases, as found by Elkinton, Winkler et al. in dogs.<sup>3, 4</sup> The possible benefit of potassium replacement therapy should be emphasized.

*Alkalization in Sulfonamide Therapy:* In preventing renal damage from sulfonamides, the value of routine adjuvant alkali therapy is debatable. The various renal lesions to be considered are outlined in table 1. Of these lesions, only Group I, the crystallurias, are preventable by the use of alkali. Sulfonamides and their esters are relatively insoluble in an acid urine and the crystals can cause irritation, hematuria and obstruction at any point from the tubules to the bladder. Sodium bicarbonate, or sodium r-lactate, given in sufficient dosage of 12 to 22 gm. daily has been shown to decrease or eliminate crystalluria by raising the pH of the urine to at least 7.5 at which point the sulfonamides are quite soluble.<sup>13-15</sup> However, even obstructive anuria with uremia, the most serious complication of crystalluria, may be readily treated by ureteral lavage or nephrostomy, usually with complete recovery.<sup>11</sup> An adequate fluid intake and avoidance of overdosage by determinations of the blood sulfonamide level will also help greatly to prevent these reactions.

The more serious sulfonamide nephropathies, toxic nephrosis<sup>16-19</sup> and those due to hypersensitivity,<sup>20-22</sup> often lead to irreversible renal damage if not a direct fatality (table 1, Groups II and III). These lesions are apparently unrelated to crystalluria, however, and their incidence is not decreased by the use of alkali, judging from a review of the larger series of experimental and clinical studies.<sup>16-19, 22-26</sup> On the contrary, Earle has shown that sodium bicarbonate greatly increases the tubular excretion of sulfamerazine, lowering the blood level so that a higher dosage is required and thus increasing the total exposure of the tubular cells to this toxic agent.<sup>27</sup>

\* Patients with renal disease show a pathological tendency to divert salt and fluid from the blood into the tissues even with a body electrolyte content which is usually normal or low. For example, most nephritics are unable to develop the transient hydremia of approximately 4 per cent which is seen in normals after the ingestion of hypertonic saline solution.<sup>10</sup> Such salt solutions are taken up almost immediately by the tissues to form edema fluid in the nephritic, without even a transiently detectable hydremia. This fact might explain why even salt-free fluids greatly in excess of the urine output could alone carry a patient with renal insufficiency from a state of hyperchloremic dehydration over to one of generalized edema at a normal or low serum chloride level.

TABLE I

## Renal Lesions Due to Sulfonamide Drugs

- I. *Crystalluria* (obstructive and irritative, due to deposits of drug insoluble in an acid urine)
    - A. *Extraneuphric* (calyces, pelves, ureters, bladder) <sup>28-30</sup>
      - Persistent renal calculi <sup>31</sup>
      - Radio-opaque membranous pyelitis <sup>32</sup>
    - B. *Intranephric* (tubules and rarely glomeruli) <sup>18, 19</sup>
  - II. *Toxic Nephrosis* (focal or diffuse tubular damage without demonstrable crystalline deposits)
    - A. Nephrosis with uremia, oliguria, and normal or low chlorides <sup>16-19</sup>
    - B. Nephrosis with uremia, hyperchloremia and encephalopathy (Luetscher and Blackman <sup>1</sup>)
 Associated lesions:
    1. Glomerular damage (rare) <sup>1, 10</sup>
    2. Thrombosis of adjacent interlobular veins <sup>1, 5, 17</sup> (see IIIB) \*
  - III. *Lesions of Hypersensitivity* (disseminated focal lesions in the kidneys and other organs)
    - A. Periarthritis nodosa <sup>20-22</sup>
    - B. Focal thrombophlebitis,\* renal interlobular and splenic trabecular veins <sup>1, 5</sup>
    - C. Focal disseminated interstitial necrosis
      1. Miliary granulomata <sup>5, 17, 19, 33</sup>
      2. Acute miliary aseptic necrosis <sup>34-36</sup>
- (Combinations of many of the above lesions have been reported)

\*Luetscher and Blackman <sup>1</sup> felt that focal thrombophlebitis was due to contact of the damaged tubule and irritative drug with the wall of an adjacent vein, while Maisel, Kubik and Ayer <sup>5</sup> considered it to be a part of a more generalized sensitivity reaction.

Alkalization of the urine, therefore, is probably of questionable value except in preventing the relatively innocuous renal sulfonamide reactions which involve crystalluria, and then only when given in a very high sustained dosage. A proper selection of cases for sulfonamide therapy, an adequate fluid intake and a proper regulation of dosage by determinations of the blood sulfonamide level are the obvious precautions which should help most to lower the incidence of serious or fatal sulfonamide nephropathies.

## SUMMARY

A fatal case of toxic nephrosis following the administration of only 4 gm. of oral sulfadiazine, associated with hyperchloremia and encephalopathy, has been presented. The rapid exitus with a cerebral type of hyperpyrexia and shock, without evidence of cardiac failure or pulmonary edema, suggests that the encephalopathy may have been a major cause of death. A direct relationship between encephalopathy and hyperchloremia per se, however, cannot be proved in this case. Early diagnosis of hyperchloremia by frequent determinations of the serum chloride level is important in such cases of acute renal disease before irreversible changes from intracellular dehydration can occur. Since the mechanism of hyperchloremia consists of a selective water diuresis with continued sodium and chloride retention, it is not encountered during the initial stage of anuria in toxic nephrosis but rather during the diuresis of recovery. During the hyperchloremic syndrome a subsiding azotemia, minimal acidosis and a moderate or large urine volume with a very low fixed concentration of sodium and chloride may be found.

Specific therapy includes the maximum amount of salt-free fluids which can be tolerated without the appearance of pulmonary or generalized edema, usually 3 to 5 liters daily, preferably intravenously. As soon as the hyperchloremic de-

hydration has been controlled the volume of fluid intake should usually be promptly restricted, depending upon the urine output, in order to avoid over-treatment to the point of causing generalized edema.

Potassium replacement therapy may well be indicated, judging from the evidence of generalized intracellular potassium deficiency in experimental hyperchloremia in dogs.

This case once more illustrates the potential dangers of sulfonamide therapy, even in small oral doses, and the ineffectiveness of routine alkali administration in preventing a fatal sulfonamide nephrosis.

#### ADDENDUM

Since this report was completed, two additional cases of hyperchloremia and hypernatremia without marked acidosis, have been observed at the Peter Bent Brigham Hospital. Both cases showed a toxic encephalopathy. One followed the use of sulfathiazole, and was also referred from a psychopathic hospital, having shown initially a predominance of psychotic symptoms. The other case occurred following severe gastrointestinal hemorrhage, and will be reported in detail by Merrill and his associates, among a series of patients treated by means of a modified Kolff artificial kidney.<sup>37</sup>

#### BIBLIOGRAPHY

1. LUETSCHER, J. A., and BLACKMAN, S. S., JR.: Severe injury to kidneys and brain following sulfathiazole administration: high serum sodium and chloride levels and persistent cerebral damage, *Ann. Int. Med.*, 1943, xviii, 741-756.
2. GAMBLE, J. L.: Extracellular fluid, a lecture syllabus, Department of Pediatrics, Harvard Medical School, 1942.
3. WINKLER, A. W., ELKINTON, J. R., HOPPER, J., JR., and HOFF, H. E.: Experimental hypertonicity: alterations in body water and cause of death, *Jr. Clin. Invest.*, 1944, xxiii, 103-109.
4. ELKINTON, J. R., and WINKLER, A. W.: Transfer of intracellular potassium in experimental dehydration, *Jr. Clin. Invest.*, 1944, xxiii, 93-102.
5. MAISEL, B., KUBIK, C. S., and AYER, J. B.: Encephalopathy, nephrosis and renal granuloma following sulfonamide therapy; case with autopsy, *Ann. Int. Med.*, 1944, xx, 311-326.
6. KINSEY, R. E.: Psychosis due to sulfonamides, *Ann. Int. Med.*, 1943, xix, 795-798.
7. FISHER, J. H., and GILMOUR, J. R.: Encephalomyelitis following administration of sulfanilamide with note on histological findings, *Lancet*, 1939, ii, 301-305.
8. ROSEMAN, E., and ARING, C. D.: Encephalopathy associated with sulfamethylthiazole therapy, *N. E. Jr. Med.*, 1941, ccxxiv, 416-420.
9. BLANKENHORN, M. A.: Multiple peripheral neuritis occurring with sulfonamide therapy, *Ann. Int. Med.*, 1944, xx, 423-430.
10. LITTLE, S. C.: Nervous and mental effects of sulfonamides, *Jr. Am. Med. Assoc.*, 1942, cxix, 467-474.
11. STYRON, C. W., and LEADBETTER, W. F.: The treatment of anuria, *N. E. Jr. Med.*, 1944, ccxxx, 721-728.
12. KUGEL, V. H.: Management of acute toxic nephrosis, *Am. Jr. Med.*, 1947, iii, 188-205.
13. FOX, C. L., JR., JENSEN, O. J., JR., and MUDGE, G. H.: Prevention of renal obstruction during sulfadiazine therapy, *Jr. Am. Med. Assoc.*, 1943, cxxi, 1147-1150.
14. GILLIGAN, D. R., GARB, S., WHEELER, C., and PLUMMER, N.: Adjuvant alkali therapy in the prevention of renal complications from sulfadiazine, *Jr. Am. Med. Assoc.*, 1943, cxxii, 1160-1165.
15. PENNA, O. J., and CHRISTOPHER, F.: Alkalization of urine during sulfonamide therapy, *Jr. Am. Med. Assoc.*, 1946, cxxx, 1067-1069.

16. ENDICOTT, K. M., and KORNBERG, ARTHUR: A pathological study of renal damage produced by sulfadiazine in rats, *Am. Jr. Path.*, 1945, xxi, 1091-1099.
17. MAISEL, B., McSWAIN, B., and GLENN, F.: Lesions produced with sulfadiazine, *Proc. Soc. Exper. Biol. and Med.*, 1942, xlix, 715-717.
18. PRIEN, E. L.: Mechanism of renal complications in sulfonamide therapy, *N. E. Jr. Med.*, 1945, ccxxii, 63-68.
19. MURPHY, F. A., KUZMA, J. F., POLLEY, T. Z., and GRILL, J.: Clinicopathologic studies of renal damage due to sulfonamide compounds; report of 14 cases, *Arch. Int. Med.*, 1944, lxxiii, 433-443.
20. RICH, A. R.: Rôle of hypersensitivity in periarteritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy, *Bull. Johns Hopkins Hosp.*, 1942, lxxi, 123-140.
21. RICH, A. R.: Additional evidence of the rôle of hypersensitivity in the etiology of periarteritis nodosa. Another case associated with a sulfonamide reaction, *Bull. Johns Hopkins Hosp.*, 1942, lxxi, 375-379.
22. RICH, A. R., and GREGORY, J. E.: Experimental demonstration that periarteritis nodosa is manifestation of hypersensitivity, *Bull. Johns Hopkins Hosp.*, 1943, lxxii, 65-88.
23. FINLAND, M., STRAUSS, E., and PETERSON, O. L.: Sulfadiazine; therapeutic evaluation and toxic effects on 446 patients, *Jr. Am. Med. Assoc.*, 1941, cxvi, 2641-2647.
24. PLUMMER, N., and WHEELER, C.: Toxicity of sulfadiazine; observations on 1357 cases, *Am. Jr. Med. Sci.*, 1944, ccvii, 175-184.
25. VILTER, C. F., and BLANKENHORN, M. A.: Toxic reactions of newer sulfonamides, *Jr. Am. Med. Assoc.*, 1944, cxxvi, 691-695.
26. WHEELER, C., and PLUMMER, N.: Sulfadiazine and sodium sulfadiazine; comparison of certain of their clinical and pharmacologic values, *Ann. Int. Med.*, 1942, cvi, 269-285.
27. EARLE, D. P., JR.: Renal excretion of sulfamerazine, *Jr. Clin. Invest.*, 1944, xxiii, 914-920.
28. BRADFORD, H. A., and SHAFFER, J. H.: Renal changes in a case of sulfadiazine anuria, *Jr. Am. Med. Assoc.*, 1942, cxix, 316-318.
29. GROSS, P., COOPER, F. B., and SCOTT, R. E.: Urolithiasis medicamentosa, *Urol. and Cutan. Rev.*, 1940, xliv, 205-209.
30. TREVETT, G. I., and BLACKMAN, S. S., JR.: Source of sulfathiazole hematuria induced in rabbits, *Ann. Int. Med.*, 1944, xx, 971-980.
31. NEWMAN, H. R., and SHLESER, I. H.: Sulfonamide renal calculus surgically removed two years after administration of sulfapyridine, *Jr. Urol.*, 1942, xlvii, 258-261.
32. ADAMS, PAYSON: Radiopaque membranous pyelitis following sulfonamide therapy, *Jr. Am. Med. Assoc.*, 1943, cxxii, 419-423.
33. FRENCH, A. J., and WELLER, C. V.: Interstitial myocarditis following clinical and experimental use of sulfonamide drugs, *Am. Jr. Path.*, 1942, xviii, 109-121.
34. MERKEL, W. C., and CRAWFORD, R. C.: Pathologic lesions produced by sulfathiazole, *Jr. Am. Med. Assoc.*, 1942, cxix, 770-776.
35. RAKE, G., VAN DYKE, H. B., and CORWIN, W. C.: Pathologic changes following prolonged administration of sulfathiazole and sulfapyridine, *Am. Jr. Med. Sci.*, 1940, cc, 353-361.
36. LEDERER, M., and ROSENBLATT, P.: Death during sulfathiazole therapy; pathological and clinical observations on four cases with autopsies, *Jr. Am. Med. Assoc.*, 1942, cxix, 8-18.
37. MERRILL, J. P., SMITH, S. S., CALLAHAN, E. J., and THORN, G. W.: Clinical application of an artificial kidney, Part II, in press.

## EDITORIAL

### AMINOPTERIN IN THE TREATMENT OF ACUTE LEUKEMIA

THE inhibition of the biological activity of an essential metabolite by compounds which are structurally related to it is now a well known phenomenon. The underlying principles believed to be involved and their importance in the study of fundamental metabolic processes have previously been discussed in this journal.<sup>1</sup> Folic acid (pteroyl glutamic acid) and its specific antagonists constitute one of the most carefully studied examples of this relationship. By an antagonist in this sense is meant a substance which will inhibit the growth of *Lactobacillus casei* in a suitable culture medium containing barely adequate amounts of folic acid, but whose inhibitory action can be overcome by adding more folic acid to the medium. Within appropriate quantitative limits, a similar antagonism can be demonstrated in experimental animals.

Stimulated by the observations of Lewisohn and associates that *L. casei* fermentation factor (containing pteroyltriglutamic acid) frequently caused regression of certain breast cancers in mice, Farber et al.<sup>2</sup> administered this material to human subjects with various types of inoperable malignant tumors. In certain cases it seemed to be beneficial in causing subjective improvement and diminution in size of the tumor. When given to cases of acute leukemia, however, it seemed to accelerate and aggravate the process. This led them to try the effect of folic acid antagonists, and in 1948<sup>3</sup> they reported obtaining temporary remissions in 10 of 16 cases of acute leukemia. These observations aroused widespread interest, and folic acid antagonists have been employed on an experimental basis in the treatment of acute leukemia in many clinics. Several different compounds have been used with more or less effect, but at present the most potent and most extensively employed is aminopterin (4-aminopteroyl glutamic acid).

Farber<sup>4</sup> has since summarized the results obtained by his group. Of about 60 children treated for three weeks or longer, somewhat over 50 per cent showed clinical or hematological improvement or both. Reports of other observers have in general confirmed Farber's observations that remissions may be obtained, but the frequency of such remissions has varied greatly in different clinics.

Dameshek and his associates<sup>5</sup> have studied a series of 34 cases, chiefly

<sup>1</sup> SACKS, M. S.: Biologic competition between structurally related compounds, Editorial, Ann. Int. Med., 1949, xxx, 867-870.

<sup>2</sup> FARBER, S., et al.: The action of pteroyl glutamic conjugates on man, Science, 1947, cvi, 619-621.

<sup>3</sup> FARBER, S., et al.: Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl glutamic acid (aminopterin), New England Med. Jr., 1948, ccxxxviii, 787-793.

<sup>4</sup> FARBER, S.: Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer, Blood, 1949, iv, 160-167.

<sup>5</sup> DAMESHEK, W.: The use of folic acid antagonists in the treatment of acute and subacute leukemia, Blood, 1949, iv, 168-171.

in adults. Of these eight died within five days and were virtually untreated. Of the 26 surviving for a longer period, nine or 34 per cent had remissions. Wolman et al.<sup>6</sup> reported remissions in seven of eight cases of acute leukemia. More recently Stickney et al.<sup>7</sup> from the Mayo Clinic observed complete remissions lasting up to four months in five of 21 children and in three of 33 adults. Partial remissions were obtained in eight additional cases (five children and three adults).

On the other hand Conley<sup>8</sup> obtained no remissions in nine cases of acute leukemia so treated. In seven cases there was a fall in the total leukocyte count, but abnormal cells did not disappear from the blood, the marrow continued to show a leukemic pattern, and there was no striking clinical improvement. The results in a larger series of cases subsequently treated have not been materially different.<sup>9</sup> Meyer et al.<sup>10</sup> obtained clinical and hematological improvement in only four of 43 cases. In 15 cases treatment was stopped because of severe toxic effects of the drug, and 24 cases were not materially affected.

The reason for such divergent results is not evident. The criteria of a remission employed by various observers may differ. It is questionable whether the failure to obtain remissions is due merely to inadequate dosage, since toxic reactions were common in these series. However, the margin between an effective dose and a dangerously toxic dose is at times very narrow, and the more successful observers may have continued treatment with greater hardihood in spite of alarming toxic symptoms.

In cases obtaining a satisfactory remission there have been marked subjective improvement, subsidence of fever and bleeding and an increase in strength so that within two or three weeks certain patients have been able to resume normal activities. There is a reduction in the total leukocyte count to normal or even to leukopenic levels. The primitive cells diminish in number or may disappear from the blood, so that it appears normal. The bone marrow tends to revert toward a normal pattern with a marked diminution in the percentage of blast cells. Some have reported that films of the marrow became normal, whereas others found some abnormality persisting. There may be an erythrocytic hyperplasia with the appearance of megaloblasts in the marrow, as might be expected with a deficiency of folic acid. With this there may be a rise in the red cell count and an increase in blood platelets. There may be a diminution in the size of the lymph nodes and spleen which is sometimes very marked.

Such remissions may last for a few weeks or months, but as a rule aminopterin must be continued in a reduced maintenance dose or a relapse

<sup>6</sup> WOLMAN, I. J., et al.: Leukemia in childhood. Preliminary report of response to aminopterin, *Pennsylvania Med. Jr.*, 1949, lii, 474-481.

<sup>7</sup> STICKNEY, J. M., et al.: The treatment of acute leukemia with folic acid antagonists, *Proc. Staff Meet., Mayo Clin.*, 1949, xxiv, 525-533.

<sup>8</sup> CONLEY, C. L.: Aminopterin in the treatment of acute leukemia (abstract), *Bull. Johns Hopkins Hosp.*, 1949, lxxxiv, 395.

<sup>9</sup> Personal communication.

<sup>10</sup> MEYER, L. M., et al.: Aminopterin (a folic acid antagonist) in the treatment of leukemia, *Am. Jr. Clin. Path.*, 1949, xix, 119-126.

quickly follows. If a relapse occurs, resumption of a full dose may bring about further remissions. Patients have been maintained in reasonably good condition in this way for many months, and one case for nearly two years. Eventually, however, either they fail to respond to aminopterin or grave toxic symptoms necessitate terminating treatment, the disease progresses, and death ensues. No case has been cured. Aminopterin seems to be ineffective in chronic myeloid leukemia.<sup>7, 11</sup>

Aminopterin is a potent and very dangerous drug, and its effects are by no means limited to the hemopoietic tissues. Toxic manifestations are frequent and often severe. In many cases they are unavoidable if an effective dose is administered. One of the commonest is an ulcerative stomatitis which is often but not invariably associated with a leukopenia. Manifestations of a gastroenteritis are also frequent. More serious are profuse hemorrhages, especially from the nose and gastrointestinal tract, which may be uncontrollable. Leukopenia is common, and there may be an extreme granulocytopenia with increasing anemia and thrombocytopenia, associated with hypoplasia of the marrow which may be irreversible. Cutaneous eruptions have been described in severe cases. Among occasional minor manifestations may be mentioned alopecia and deafness.

Ulcerations of the buccal mucous membranes and hemorrhages are common manifestations of the disease and do not necessarily contraindicate treatment with aminopterin. In patients who are under treatment, however, it may be difficult to determine whether such symptoms are referable to the disease or to the drug.

Individual susceptibility to aminopterin varies, and the dose has to be adjusted for each case. Severe toxemia may appear abruptly. It often subsides, however, if aminopterin is stopped promptly and suitable treatment administered (folic acid, transfusion, antibiotics).

There are obvious difficulties in interpreting the results of treatment in these cases. Spontaneous remissions occur occasionally in acute leukemia. The frequency with which they occur is not known precisely, but Diamond's<sup>4</sup> estimate of 10 per cent is probably a maximum figure. Furthermore spontaneous remissions as complete and long lasting as those described in some of the reported cases are quite rare. There can be little doubt that aminopterin has favorably influenced the course of the disease and that its effect is much more definite than that of the other procedures which have been previously employed.

It is equally evident, however, that aminopterin is a highly unsatisfactory therapeutic agent. Its action is unpredictable, and it is effective in only a minority of the cases. Its effect is temporary only, and no cure, nothing more than a transient remission can be hoped for. It causes serious toxic reactions, and some degree of such action must be anticipated if effective quantities are given. In many cases these reactions are prohibitively severe.

<sup>11</sup> BERMAN, L., et al.: Use of a folic acid antagonist in chronic leukemia, *Am. Jr. Clin. Path.*, 1949, xix, 127-133.



For the present, the use of aminopterin is still experimental and should properly be restricted to clinics in which the patients can be observed with great care and corrective measures instituted promptly if serious toxemia develops. Under such conditions aminopterin may justifiably be employed since it offers a reasonable prospect of prolonging life and increasing comfort in some cases.

The chief importance of this work is that it opens up a new field for investigation of the treatment of neoplastic diseases. Even if no more satisfactory antagonist to folic acid should be found, there are many other essential metabolic processes in the cells which might be influenced in a similar manner if the chemical reactions involved were precisely known. The hope is justified that some substance may be found which would act more specifically upon the metabolism of neoplastic cells and presumably be more effective and less damaging to other tissues.

P. W. C.

## REVIEWS

*Conditioned Reflexes and Neuron Organization.* By JERZY KONORSKI. 267 pages; 14.5 × 22.5 cm. Cambridge University Press, London; Macmillan Co., New York. 1948. Price, \$4.00.

This book is written by a former pupil of Pavlov's working in Poland, whose laboratory was destroyed and whose researches were interrupted by the war. The intention of the author is shown by his dedication to Pavlov and Sherrington: "... In the hope that this work will do something to bridge the gulf between their respective achievements."

It is not a book for the amateur or general reader, but is only for those who are already deeply steeped in either Pavlovian tradition or neurophysiological work.

The author takes up in detail the basic concepts of Pavlov which he considers need thorough revision, for example internal inhibition, irradiation, induction, summation, sleep, nomenclature. He feels that the material contributed by Pavlov is of enormous importance, not only in its special field but for the advancement of more strictly neurophysiological research. He claims that his concept of higher nervous activity is in harmony with general physiology of the nervous system and the neuron theory. The elaboration of a conditional reflex he thinks depends upon new functional connections in the brain and the multiplication of synapses. Unless there is repetition of excitation within a certain period the synaptic connections undergo atrophy. Internal inhibition consists in a formation of used synaptic connections of inhibitory character. The author feels that in spite of the erroneous nature of some of Pavlov's theories, the great physiologist has enormously enriched our knowledge of the nervous system and the ability to explore its intricacies in the future through the method of study of the conditional reflex.

W. HORSLEY GANTT

*Modern Practice in Psychological Medicine.* Edited by J. R. REES, M.D. 488 pages; 17 × 25 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper and Bros., New York. 1949. Price, \$10.00.

This book is a collection of papers by a group of outstanding British and Canadian psychiatrists and psychologists. The topics covered are chapter headings of what one would expect in a textbook of psychiatry. As one can expect, there is some unevenness of excellence and considerable overlapping of topics. On the whole, however, the book is timely, up-to-date and of value as a general introduction to physicians who wish to know more about the emotional aspects of their patients. The point of view on the whole is conservative and practical. The editor, Dr. J. R. Rees, writes a chapter on Psychotherapy which is full of sound and useful advice to the general practitioner.

H. W. N.

*Heart: A Physiologic and Clinical Study of Cardiovascular Diseases.* By ALDO A. LUISADA, M.D. 653 pages; 25.5 × 19 cm. The Williams and Wilkins Company, Baltimore. 1948. Price, \$10.00.

The simple but comprehensive title of this book is well chosen, for its contents are not confined to *diseases* of the heart. With a background of over 20 years of investigative and clinical cardiology, the author has a unique and intimate knowledge with which to endow his work, and a wealth of cardiac physiology is included. There

are probably no other 600 consecutive pages in print which contain so much and so diversified cardiological information.

While no aspect of the heart is overlooked, there is an admitted emphasis on "mechanized" cardiology. Thus in the description of each disorder, besides the expected discussion on electrocardiographic and radiological findings, there is an account of the changes to be found in cardiogram, pneumocardiogram, electrokymogram, arterial and venous pulse tracings, and, most particularly, in phonocardiogram.

Among the outstanding merits of this book is the exceptionally large number of excellent illustrations, especially those which present, in one form or another, graphic registrations of cardiac action. Another good point is the inclusive bibliography which covers both American and European literature. A minor criticism is that many of the illustrations would be even more valuable with fuller descriptive legends; similarly in the text, which is necessarily condensed, the author sometimes achieves brevity at the expense of clarity.

Dr. Luisada clearly has a passion for eponymy. For example, the chapter on pericardial diseases contains no less than thirty such designations, and the text in general is peppered with eponyms—from Auenbrugger's sign to Zeri's syndrome. This is a mere observation of interesting fact and is not intended to imply any criticism whatever. The preservation of historic names has much to be said for it.

Whether or not the author subscribes to its use, it is surprising to find no mention of Dicumarol in the treatment of myocardial infarction. Dr. Luisada has kept the expression of personal views within moderate limits; he gives his own explanations, however, for several circulatory phenomena, such as some of the signs of aortic insufficiency. And such views, held as they are by an exceptionally thorough investigator, must command respect and stimulate enquiry, even if they are not given ready acceptance. The author has also deviated from the "orthodox" *etiological* classification of heart disease, because he believes that this "scheme of beautiful simplicity" encourages a mental laziness in formulating exact diagnoses. Instead he has adopted a classification based on anatomical-clinical syndromes.

This book has been written "for the large group of physicians who desire to increase their knowledge of heart disease." There must be few cardiologists, and fewer internists, whose knowledge of cardiovascular physiology and pathology will not be substantially increased by a careful perusal of this informative book.

H. J. L. M.

*Human Biochemistry.* 2nd Ed. By ISRAEL S. KLEINER, Ph.D., Professor of Biochemistry and Director of the Department of Physiology and Biochemistry, New York Medical College, New York. 649 pages; 17 × 25 cm. C. V. Mosby Co., St. Louis. 1948. Price, \$7.00.

Dr. Kleiner's book was written primarily for medical students and physicians who wish to familiarize themselves with those aspects of biochemistry which pertain to the human body. It attempts to present "clinical aspects of biochemistry without usurping any clinicians' domain and without neglecting the fundamentals" of the subject. The program is an ambitious one covering as it does the basic chemistry of carbohydrates, lipids, proteins, enzymes, vitamins, hormones, as well as metabolism in its varied aspects. The book will serve the student both in his courses in biochemistry and physiology and later in his period of clinical training. The practicing physicians will find it valuable as a reference text.

E. G. S.

## BOOKS RECEIVED

Books received during October are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Advances in Pediatrics—Volume IV.* Editorial Board: S. Z. LEVINE, Cornell University Medical College, New York; ALLAN M. BUTLER, Harvard Medical School, Boston; L. EMMETT HOLT, JR., New York University, College of Medicine, New York, and A. ASHLEY WEECH, University of Cincinnati, College of Medicine, Cincinnati. 316 pages; 24 × 15.5 cm. 1949. Interscience Publishers, Inc., New York. Price, \$6.50.

*Arterial Hypertension: Its Diagnosis and Treatment.* 2nd ed. By IRVINE H. PAGE, M.D., and ARTHUR CURTIS CORCORAN, M.D., Research Division of the Cleveland Clinic Foundation, Cleveland. 400 pages; 21 × 14.5 cm. 1949. The Year Book Publishers, Inc., Chicago. Price, \$5.75.

*Bone and Joint Radiology.* By EMERIK MARKOVITS, M.D., Formerly Scientific Collaborator of the Central Radiologic Institute of the General Hospital (Holzknecht-Institute), Vienna, etc. 446 pages; 26 × 18 cm. 1949. The Macmillan Company, New York. Price, \$20.00.

*Clinical Diagnosis by Laboratory Examinations.* 2nd ed. By JOHN A. KOLMER, M.S., M.D., Dr.P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry of Temple University, etc. 1212 pages; 25.5 × 17 cm. 1949. Appleton-Century-Crofts, Inc., New York. Price, \$12.00.

*The Development of Gynaecological Surgery and Instruments: A Comprehensive Review of the Evolution of Surgery and Surgical Instruments for the Treatment of Female Diseases from the Hippocratic Age to the Antiseptic Period.* By JAMES V. RICCI, M.D., Clinical Professor of Gynaecology and Obstetrics, New York Medical College, etc. 594 pages; 27 × 18.5 cm. 1949. The Blakiston Company, Philadelphia. Price, \$12.00.

*Differential Diagnosis of Chest Diseases.* By JACOB JESSE SINGER, M.D., F.A.C.P., F.C.C.P., Medical Director of the Rose Lampert Graff Foundation, Beverly Hills, etc. 344 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, \$7.50.

*Digitalis and Other Cardiotonic Drugs.* 2nd ed. By ELI RODIN MOVITT, M.D., Chief of Medicine, Veterans Administration Hospital, Oakland, California, etc. 245 pages; 24.5 × 16 cm. 1949. Oxford University Press, New York. Price, \$5.75.

*Diseases of the Aorta: Diagnosis and Treatment.* By NATHANIEL E. REICH, M.D., F.A.C.P., Associate in Medicine, Long Island College of Medicine, etc. 288 pages; 24 × 16 cm. 1949. The Macmillan Company, New York. Price, \$7.50.

*Die Dystrophie.* By PROFESSOR DR. MED. HEINRICH BERNING. 197 pages; 24.5 × 17.5 cm. 1949. Georg Thieme Verlag, Stuttgart. Price, Halbleinen DM 18.—

*Functional Localization in Relation to Frontal Lobotomy, Being the William Withering Memorial Lectures Delivered at the Birmingham Medical School, 1948.* By JOHN F. FULTON, O.B.E., M.D., D.SC., LL.D. (Birm.). 140 pages; 21 × 13 cm. 1949. Oxford University Press, New York. Price, \$3.00.

- Golden Jubilee World Tribute to Dr. Sidney V. Haas, In Honor of His Pioneering Contribution to Celiac Therapy and the Treatment of the Hypertonic Infant, and of the Completion of His Fiftieth Year of Medical Practice.* 38 pages; 24 × 15.5 cm. 1949. The Committee for the Golden Jubilee Tribute to Dr. Sidney V. Haas, New York.
- Grundlagen der Funktionellen Urologischen Röntgendiagnostik.* By DR. MED. HABIL. WALTER PFEIFER. 88 pages; 24.5 × 17 cm. (paper-bound). 1949. Georg Thieme Verlag, Stuttgart. Price, kart DM 9.60.
- Histopathology of the Skin.* By WALTER F. LEVER, M.D., Instructor in Dermatology, Harvard Medical School, etc. 449 pages; 24 × 15.5 cm. 1949. J. B. Lippincott Company, Philadelphia. Price, \$10.00.
- Human Pathology.* 7th ed. By HOWARD T. KARSNER, M.D., LL.D., Former Professor of Pathology, Western Reserve University, etc. 927 pages; 26 × 18 cm. 1949. J. B. Lippincott Company, Philadelphia. Price, \$12.00.
- Jest What the Doctor Ordered.* By DR. FRANCIS LEO GOLDEN; with a Foreword by N. BERTRAM COLE, M.D., F.A.C.S. 256 pages; 21 × 14 cm. 1949. Frederick Fell, Inc., New York. Price, \$2.95.
- Malaria: The Biography of a Killer.* By LEON J. WARSHAW, M.D. 348 pages; 22 × 14.5 cm. 1949. Rinehart & Company, Inc., New York. Price, \$3.75.
- Minutes of the Seventh Streptomycin Conference, Held on April 21, 22, 23, & 24, 1949, Cosmopolitan Hotel, Denver, Colorado.* Prepared and Edited by Veterans Administration, Area Office, Washington, D. C. 360 pages; 26 × 20 cm. (paper-bound). 1949. Veterans Administration, Washington, D. C. Price, Not for sale—limited edition for distribution to VA hospitals and medical libraries.
- Neoplasms of the Dog.* By R. M. MULLIGAN, M.D., Professor of Pathology in the University of Colorado Medical Center School of Medicine. 135 pages; 23.5 × 15.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, \$4.00.
- Textbook of Bacteriology (Eleventh Edition of Muir & Ritchie's "Manual").* By C. H. BROWNING, M.D., LL.D., D.P.H., F.R.S., Gardiner Professor of Bacteriology, University of Glasgow, and T. J. MACKIE, C.B.E., M.D., LL.D., D.P.H., Professor of Bacteriology, University of Edinburgh. 907 pages; 25.5 × 16 cm. 1949. Oxford University Press, New York. Price, \$12.75.
- A Textbook of Medicine for Nurses.* 5th ed. By E. NOBLE CHAMBERLAIN, M.D., M.SC., F.R.C.P., Senior Lecturer in Medicine, University of Liverpool, etc.; with a Foreword by DAME ELLEN MUSSON, D.B.E., R.R.C., LL.D., Formerly Chairman, General Nursing Council for England and Wales. 491 page; 22.5 × 14 cm. 1949. Oxford University Press, New York. Price, \$6.00.
- Unipolar Lead Electrocardiography, Including Standard Leads, Augmented Unipolar Extremity Leads and Multiple Unipolar Precordial Leads, and a Section on Cardiac Arrhythmias.* 2nd ed. By EMANUEL GOLDBERGER, B.S., M.D., Adjunct Physician, Montefiore Hospital, New York. 392 pages; 24 × 15.5 cm. 1949. Lea & Febiger, Philadelphia. Price, \$7.50.

# COLLEGE NEWS NOTES

## ELECTIONS TO FELLOWSHIP AND ASSOCIATESHIP

### AMERICAN COLLEGE OF PHYSICIANS

NOVEMBER 13, 1949

(*FELLOWS, FULL CAPITALS: Associates, lower case*)

SALVADOR ACEVES .....	Mexico, D. F.
FRANK MARVIN ADAMS .....	Hot Springs Nat'l Park, Ark.
LEYLAND JOHN ADAMS .....	Montreal, Que., Can.
WRIGHT ADAMS .....	Chicago, Ill.
Clarence Mendel Agress .....	Beverly Hills, Calif.
Elmer Alpert .....	New York, N. Y.
GEORGE JOHN ANDAY .....	Chicago, Ill.
CHARLES HENRY ARMENTROUT .....	Asheville, N. C.
LEONARD MAX ASHER .....	Beverly Hills, Calif.
Allie Kearney Atkinson .....	Great Falls, Mont.
Joseph Gordon Barrow .....	Atlanta, Ga.
HYMAN ELIHU BASS .....	New York, N. Y.
Jere Marklee Bauer .....	Ann Arbor, Mich.
George Leonard Baum .....	Milwaukee, Wis. (V.A.)
EDWARD HORTON BENSLEY .....	Montreal, Que., Can.
EUGENE SYDNEY BERESTON .....	Baltimore, Md.
KARL HENRY BEYER, JR. ....	Bala-Cynwyd, Pa.
Anthony Andrew Bianco .....	New York, N. Y.
Hylan Arthur Bickerman .....	Forest Hills, N. Y.
Maxwell Jacob Binder .....	Los Angeles, Calif. (V.A.)
CECIL CLINTON BIRCHARD .....	Montreal, Que., Can.
James Bell Black, Jr. ....	Richmond, Va.
HERRMAN LUDWIG BLUMGART .....	Boston, Mass.
JOHN JAMES BOEHRER .....	Minneapolis, Minn.
WILLIAM PIERCE BOGER .....	Upper Darby, Pa.
Eli Leroy Borkon .....	Carbondale, Ill.
GEORGE ARTHUR BOYLSTON .....	Portland, Ore.
E(mory) James Brady .....	Denver, Colo.
C(HARLES) H(ENRY) HARDIN BRANCH ...	Salt Lake City, Utah
John Grierson Brazier .....	Omaha, Nebr.
Samuel Henry Brethwaite .....	Summit, N. J.
I. JAY BRIGHTMAN .....	Albany, N. Y.
(GEORGE) MALCOLM BROWN .....	Kingston, Ont., Can.
Herbert Rutherford Brown, Jr. ....	Rochester, N. Y.
James Cushing Brudno .....	Quincy, Mass.
HEINRICH GEORGE BRUGSCH .....	Boston, Mass.
JOSEPH BUDNITZ .....	Pittsfield, Mass.
Samuel Simon Burden .....	Elkins Park, Pa.
William Champlin Burrage .....	Portland, Maine
Irving Frederick Burton .....	Detroit, Mich.
Ewald William Busse .....	Denver, Colo.
Maston Kennerly Callison .....	Memphis, Tenn.
John Dodd Cameron .....	Defiance, Ohio

Wilfred Carrol .....	Newark, N. J.
Philip Robert Casesa .....	Brooklyn, N. Y. (V.A.)
Edward Philip Cawley .....	Ann Arbor, Mich.
Frederick Vincent Cerini .....	Los Angeles, Calif.
Carleton Burke Chapman .....	Minneapolis, Minn.
Richard Charet .....	Brooklyn, N. Y.
George L. Chesley .....	Bloomington, Ill.
AUSTIN BROCKENBROUGH CHINN .....	Cleveland, Ohio
Richard M. Christian .....	Rochester, N. Y.
GIRAGOS MISSAK CHURUKIAN .....	Paris, Ill.
Thomas Williams Clark .....	Philadelphia, Pa.
Jonas Harold Cohen .....	Baltimore, Md.
James Anthony Collins, Jr. ....	Riverside, Pa.
CHARLES ASHLEY RICHARD CONNOR .....	New York, N. Y.
Harold Herbert Coppersmith .....	New York, N. Y.
Allen Lee Cornish .....	Lexington, Ky.
Edgar Francis Cosgrove .....	Pittsburgh, Pa.
Lester Orville Crago .....	M. C., U. S. Army
Harry Isaac Cramer .....	Montreal, Que., Can.
William James Cromartie .....	McKinney, Tex. (V.A.)
JAMES HENRY CULLEN .....	Yonkers, N. Y.
George Hardin Curfman, Jr. ....	Denver, Colo.
Robert Jesse Dancey .....	Milwaukee, Wis.
THADDEUS STANLEY DANOWSKI .....	Pittsburgh, Pa.
Guy Wilson Daugherty .....	Rochester, Minn.
Lindon Lee Davis .....	East Williston, N. Y.
Charles Joseph Deere .....	Memphis, Tenn.
James Newton DeLamater .....	Alhambra, Calif.
JOHN SINCLAIR DENHOLM .....	New York, N. Y.
Emmanuel Deutsch .....	Boston, Mass.
Daniel Diamond .....	Brooklyn, N. Y.
MACDONALD DICK .....	Durham, N. C.
Lewis Dickar .....	Brooklyn, N. Y.
HELEN AIRD DICKIE .....	Madison, Wis.
William Arthur Dinsmore, Jr. ....	M.C., U. S. Navy
Francis Michael Dougherty .....	Pottsville, Pa.
Morris Dressler .....	Hartford, Conn. (V.A.)
Hugh Leo Dwyer, Jr. ....	New Haven, Conn.
Robert Slaughter Dyer .....	Louisville, Ky.
Max Ellenberg .....	New York, N. Y.
A(dam) B(rown) Curry Ellison .....	Charleston, W. Va.
Carl Charles Epstein .....	Oakland, Calif. (V.A.)
Abraham Falk .....	Minneapolis, Minn. (V.A.)
LESLIE HILLEL FARBER .....	San Francisco, Calif.
Omār John Fareed .....	Beverly Hills, Calif.
Ralph Eugene Faucett .....	M. C., U. S. Navy
Daniel Jared Feldman .....	New York, N. Y.
ARTHUR NATHANIEL FLEISS .....	Syracuse, N. Y.
Charles Cauldwell Foote .....	New York, N. Y.
Wiley Lewis Forman .....	Columbus, Ohio
James Thomas Fowler, Jr. ....	M. C., U. S. Navy
THEODORE T. FOX .....	New York, N. Y.

Murray Franklin	Iowa City, Iowa
JOSEPH THEODORE FREEMAN	Philadelphia, Pa.
Harold Aaron Friedman	Rochester, N. Y.
Murray Marcus Friedman	Santa Fe, N. M.
HAROLD FRUCHTER	Long Island City, N. Y.
CHARLES WATSON FULLERTON	Montreal, Que., Can.
Jabez Galt	Dallas, Tex.
E(dward) Philip Gelvin	New York, N. Y.
JACQUES GENEST	Montreal, Que., Can.
Joseph Gennis	New Rochelle, N. Y. (V.A.)
Charles Everett Gerson	Dayton, Ohio
James Alan Longmore Gilbert	Moose Jaw, Sask., Can.
Sidney Gilbert	Flushing, N. Y.
John Stuart Gilson	Great Falls, Mont.
Charles Harold Gingles	M. C., U. S. Army
Samuel Glassman	New York, N. Y. (V.A.)
Henry Goebel, Jr.	Bethlehem, Pa.
Jacob Goldberg	Castle Point, N. Y. (V.A.)
MORTON LOUIS GOLDHAMER	Cleveland, Ohio
Morris Irving Goldin	Detroit, Mich.
Michael Louis Gompertz	New Haven, Conn.
IRVING ISRAEL GOODOF	Auburn, Maine
Alvin Joseph Gordon	New York, N. Y.
John Edgar Gordon	Lebanon, Pa. (V.A.)
Philip Morris Gottlieb	Philadelphia, Pa.
Alexander Gotz	Ann Arbor, Mich.
SAMUEL U. GREENBERG	New York, N. Y.
Laurence Abraham Grossman	Nashville, Tenn.
Charles Michael Gruber, Jr.	Drexel Hill, Pa.
JOHN HINER GUSS	Staunton, Va.
GERALD WINTER HALPENNY	Montreal, Que., Can.
Henry Edward Hamilton	Iowa City, Iowa
Courtney Norfleet Hamlin	Rockford, Ill.
George Wesley Hammel	El Dorado, Kans.
Laura Hare	Indianapolis, Ind.
John D. Hartigan	Omaha, Nebr.
Eslie Hartman	Chicago, Ill.
George Harvey, Jr.	Jackson, Miss.
JOSEPH PAUL HARVEY	Youngstown, Ohio
Elmer Russell Hayes	Minneapolis, Minn.
ELWYN LINDLEY HELLER	Pittsburgh, Pa.
Lowell Lawrence Henderson	Urbana, Ill.
Frederick Harrison Hesser	Iowa City, Iowa
Albert Heyman	Atlanta, Ga.
JOSEPH SPURGEON HIATT, JR.	McCain, N. C.
Samuel Gaston Hibbs	Tampa, Fla.
Eugene Hildebrand	Great Falls, Mont.
GLENN IVAN HILLER	Highland Park, Mich.
John Hendricks Hodges	Philadelphia, Pa.
Martin Mandell Hoffman	Montreal, Que., Can.
George Hollander	Philadelphia, Pa.
Irving Nathan Holtzman	Brooklyn, N. Y.
Ralph E. Homann, Jr.	Los Angeles, Calif.



John Williams Hooker .....	Wilmington, Del.
Harry Aloysius Horstman, Jr. ....	M. C., U. S. Army
Dorothy Millicent Horstmann .....	New Haven, Conn.
Harvey Horwitz .....	Chicago, Ill.
John Wade Howard .....	Wilmington, Del.
KYRAN EMMETT HYNES .....	Seattle, Wash.
Lucien Waterman Ide .....	St. Joseph, Mo.
Irving Innerfield .....	Nyack, N. Y.
Albert Jackson .....	Wadsworth, Kans. (V.A.)
Alvah Rudolph Jenkins .....	Englewood, N. J.
Herbert William Jenkins .....	Sacramento, Calif.
ARTELL EGBERT JOHNSON .....	New York, N. Y.
C(ARL) HAROLD JOHNSON .....	Gettysburg, Pa.
Corbet Stephens Johnson .....	Waverly, N. Y.
Arthur Harvey Joistad, Jr. ....	Muskegon, Mich.
GRANVILLE LILLARD JONES .....	Williamsburg, Va.
Theodore Reid Jones .....	Kansas City, Mo.
Carl John Josephson .....	Denver, Colo.
Alfred Kahn, Jr. ....	Little Rock, Ark.
Frank Kaminsky .....	Brooklyn, N. Y.
Walter Fred Kammer .....	Muncie, Ind.
Irving Joseph Kane .....	New York, N. Y.
ROBERT MANOAH KARK .....	Oak Park, Ill.
Bernard Leon Kartin .....	New Haven, Conn.
SOL KATZ .....	Washington, D. C.
PAUL KAUFMAN .....	New York, N. Y.
Ernest Ellsworth Keet, Jr. ....	Queens Village, N. Y.
William Hilliary Keffer .....	Reading, Pa.
William Ernest Kelley .....	Omaha, Nebr.
William Roland Kennedy .....	Montreal, Que., Can.
Morley Job Kert .....	Los Angeles, Calif.
Harry Kessler .....	New York, N. Y. (V.A.)
John Harvey Killough .....	M. C., U. S. Navy
ROBERT COOKE KIMBROUGH, JR. ....	Knoxville, Tenn.
John Anthony Kinczel .....	Trenton, N. J.
Herbert Arthur King .....	Durham, N. C.
Stuart Dawson King .....	North Hollywood, Calif.
Dunham Kirkham .....	Togus, Maine (V.A.)
GERALD KLATSKIN .....	New Haven, Conn.
ARTHUR KLEIN .....	Richmond, Va.
Leon Arthur Kochman .....	Baltimore, Md.
HAROLD WILLIS KOHL .....	Tucson, Ariz.
Abraham Kolodin .....	Bloomfield, N. J.
ROY RACHFORD KRACKE .....	Birmingham, Ala.
Harold Maurice Kramer .....	Louisville, Ky.
Jackson Edmund Kress .....	Missoula, Mont.
William Charles Kuzell .....	San Francisco, Calif.
THOMAS HARRISON LAMBERT .....	La Jolla, Calif.
RICHARD LANGENDORF .....	Chicago, Ill.
ANTHONY JOSEPH LANZA .....	New York, N. Y.
Maurice Kamm Laurence .....	Swampscott, Mass.
Edgar Athaleston Lawrence .....	New York, N. Y.

David Lehr .....	New York, N. Y.
Stephen Howard Leslie .....	New York, N. Y.
Eli Allen Leven .....	Rochester, N. Y.
Herbert Melville Levenson .....	Framingham, Mass.
Matthew Levine .....	New York, N. Y.
Samuel Marrel Levit .....	Philadelphia, Pa.
William Likoff .....	Philadelphia, Pa.
JOSEPH FRANCIS LINSMAN .....	Beverly Hills, Calif.
EMANUEL WILLIAM LIPSCHUTZ .....	Brooklyn, N. Y.
Lester Lipson .....	Monticello, N. Y.
Jesse Cone Lockhart .....	Peoria, Ill.
HARRY JOSEPH LOWEN .....	New York, N. Y.
John Morgan Lyon .....	Englewood, Colo.
WILLIAM CHARLES MACDONALD .....	St. Louis, Mo.
Thomas Keith MacLean .....	Vancouver, B. C., Can.
Harold Haze Macumber .....	Chichasha, Okla.
Frank Joseph Manganaro .....	Kirkwood, Mo.
Sydney Gerald Margolin .....	New York, N. Y.
Jerome David Markham .....	Richmond, Va.
THOMAS WILLIAM MATTINGLY .....	M. C., U. S. Army
EDWARD MATZGER .....	San Francisco, Calif.
Edward Schuyler McCabe .....	Philadelphia, Pa.
Marcus Denney McDivitt .....	Pittsburgh, Pa.
Douglas Francis McDowell .....	Santa Barbara, Calif.
Charles Joseph McGee .....	Brockton, Mass.
FRANK BARTLETT McGLONE .....	Denver, Colo.
Arthur Joseph McSteen .....	Greensburg, Pa.
Edward Idel Melich .....	Largo, Fla. (V.A.)
Patterson Morris Menlowe .....	McKeesport, Pa.
Arthur Jesse Merrill .....	Atlanta, Ga.
John Putnam Merrill .....	Waban, Mass.
William Josef Messinger .....	New York, N. Y.
John Wright Middleton .....	Galveston, Tex.
Ernest Boyd Millard, Jr. ....	Rochester, N. Y.
Solomon Samuel Mintz .....	Philadelphia, Pa.
HOWARD SCOTT MITCHELL .....	Montreal, Que., Can.
Frank Corbin Moister .....	Hanover, N. H.
ROLLEN WAYNE MOODY .....	Denver, Colo.
J(oseph) Lloyd Morrow .....	Passaic, N. J.
Paul Vanderhoff Morton .....	San Jose, Calif.
Jack Duane Myers .....	Durham, N. C.
SAMUEL MYERSON .....	Bay Pines, Fla. (V.A.)
Max J. Nareff .....	Jamaica, N. Y.
Maurice Nataro .....	Louisville, Ky. (V.A.)
John Robert Neefe .....	Philadelphia, Pa.
Jack Nelson .....	New York, N. Y.
JAMES DAVID NELSON .....	Spartanburg, S. C.
Carl Robert Newman .....	Redwood City, Calif.
Robert H. Nickau .....	Jacksonville, Fla.
Joseph Henry Nicholson .....	Lawrence, Mass.
Joseph Mazarin Oppenheim .....	Detroit, Mich.
James Archer Orbison .....	M. C., U. S. Army

Norman Williston Osher .....	Milwaukee, Wis.
Henry Stoddert Parker .....	M. C., U. S. Army
John Lawrence Parnell .....	Vancouver, B. C., Can.
Arpad Pauncz .....	Lyons, N. J. (V.A.)
John Strother Pearson .....	Huntington, W. Va.
SIDNEY LINCOLN PENNER .....	Stratford, Conn.
Arnold Zachary Pfeffer .....	New York, N. Y.
Robert Toms Pigford .....	Wilmington, N. C.
FRANK P. PIGNATARO .....	Red Bank, N. J.
Howard Freeman Polley .....	Rochester, Minn.
Eduardo R. Pons, Jr. ....	Santurce, P. R.
Rolf Falk Poser .....	Columbus, Wis.
F(RANK) KENNETH POWER .....	Salem, Ore.
John Alan Prior .....	Columbus, Ohio
Fellowes Morgan Pruyn .....	Mount Kisco, N. Y.
Gordon Woodrow Raleigh .....	Evanston, Ill.
L(ELAND) PAUL RALPH .....	Grand Rapids, Mich.
Sanford MacArthur Rathbun .....	Beatrice, Nebr.
WALTER REDISCH .....	Jackson Heights, N. Y.
Samuel Boswell Reich .....	Hackensack, N. J.
GEORGE HENRY REIFENSTEIN .....	Syracuse, N. Y.
NORMAN REITMAN .....	New Brunswick, N. J.
RAY(MOND) LESTER RICE .....	Milwaukee, Wis.
Allen David Riemer .....	Denver, Colo.
William Henry Riser, Jr. ....	Birmingham, Ala.
DANIEL CHRISTOPHER RIVERS .....	Cincinnati, Ohio
Milton Herbert Robbins .....	New York, N. Y.
HOBERT ROGERS .....	Oakland, Calif.
Harry Evan Rollings .....	Savannah, Ga.
Alvin Abe Rosenberg .....	Morristown, N. J.
Homer Rosenberger, Jr. ....	Whittier, Calif.
HAROLD ROSENBLUM .....	San Francisco, Calif.
JACOB ALVIN ROSENKRANTZ .....	Mount Vernon, N. Y. (V.A.)
HENRY CARL ROSENSTIEL .....	Albuquerque, N. M. (V.A.)
John Bruce Ross .....	Washington, D. C.
JOSEPH FOSTER ROSS .....	Brookline, Mass.
Ralph Dinsmore Ross .....	M. C., U. S. Navy
Harold Philmore Roth .....	Shaker Heights, Ohio (V.A.)
Oscar Roth .....	New Haven, Conn.
SAUL DAVID ROTTER .....	West Palm Beach, Fla.
John Henry Rowland .....	New Brunswick, N. J.
Sidney Rubin .....	Topeka, Kans. (V.A.)
Wayne Rundles .....	Durham, N. C.
S(amuel) Senior Sack .....	Flushing, N. Y.
W(oodrow) Wilson Schier .....	Boston, Mass.
Burton Lewis Schmier .....	Detroit, Mich.
Adolph Benedict Schneider, Jr. ....	Cleveland, Ohio
Joseph Henry Schwab .....	Woodhaven, N. Y.
Joseph Atlas Schwartz .....	Atlanta, Ga. (V.A.)
Wirt Stanley Scott, Jr. ....	Stockton, Calif.
ISIDOR SILBERMANN .....	New York, N. Y.
Charles Silverberg .....	St. Louis, Mo.

ROGER GRAHAM SIMPSON .....	San Francisco, Calif.
John Clark Slaughter, Jr. ....	Evansville, Ind.
(FREDERICK) McIVER SMITH .....	Montreal, Que., Can.
Glen T. Smith .....	New York, N. Y.
Maurice Snyder .....	Salina, Kans.
Arnold Stanton .....	Richmond Hill, N. Y.
Louis Wells Staudt .....	Ann Arbor, Mich.
James Milton Steele .....	Jamestown, N. Y.
LAWRENCE IRVING STELLAR .....	Newton Center, Mass.
Edward Amberg Stern .....	Rochester, N. Y.
Marvin Stern .....	Brooklyn, N. Y.
HAROLD STEVENS .....	Washington, D. C.
Chester Pratt Stevenson .....	Fort Logan, Colo. (V.A.)
Herman Hull Stone .....	Oklahoma City, Okla. (V.A.)
THEODORE THADDEUS STONE .....	Chicago, Ill.
Lee Stover .....	Lincoln, Nebr.
Arnold Ferdinand Strauss .....	Norfolk, Va.
Benjamin Hardy Sullivan, Jr. ....	M. C., U. S. Army
CLEMENT JOSEPH SULLIVAN .....	St. Louis, Mo.
JAMES MARION SUTER .....	Abingdon, Va.
Adney Kemple Sutphin .....	Richmond, Va.
Robert Edmund Switzer .....	M. C., U. S. Navy
HENRY JOSEPH TAGNON .....	New York, N. Y.
Charles Conover Talbot .....	Chicago, Ill.
Luther Leonidas Terry .....	U. S. Public Health Service
J(oseph) Edward Tether .....	Indianapolis, Ind.
Morris Edward Thomas .....	Indianapolis, Ind.
Alexander Irwin Thomashow .....	Brooklyn, N. Y.
Charles Waters Thompson .....	Washington, D. C.
Philip Pickering Thompson, Jr. ....	Portland, Maine
Meyer C. Thorner .....	Beverly Hills, Calif.
Henry Harding Tift .....	Macon, Ga.
Philip Murry Tiller, Jr. ....	New Orleans, La.
MARTIN LOUIS TRACEY, SR. ....	Needham, Mass.
Jerome Victor Treusch .....	Beverly Hills, Calif.
Isaac Frank Tullis, Jr. ....	Memphis, Tenn.
James Lyman Tullis .....	Newton, Mass.
Walter Richard Tupper .....	North Hollywood, Calif.
GEORGE CLEVELAND TURNER .....	Chicago, Ill.
David Turnoff .....	Philadelphia, Pa.
Samuel Vaisrub .....	Winnipeg, Man., Can.
WESLEY VAN CAMP .....	Pueblo, Colo.
Paul Anton Van Pernis .....	Grand Rapids, Mich.
Helen D. Van Vactor .....	Indianapolis, Ind.
JOHN ORREN VAUGHN .....	Santa Monica, Calif.
Cristobal Alberto Vicens .....	New York, N. Y.
Leo Joseph Wade .....	University City, Mo.
ELMER GLENN WAKEFIELD .....	Rochester, Minn.
Thomas Franklin Walker, Jr. ....	Great Falls, Mont.
C(HARLES) STEWART WALLACE .....	Ithaca, N. Y.
William Bertalan Walsh .....	Washington, D. C.
William Vincent Walsh .....	North Little Rock, Ark. (V.A.)

Paul Weitz .....	Lyons, N. J. (V.A.)
William Charles Wermuth .....	Philadelphia, Pa.
Abraham Werner .....	New York, N. Y. (V.A.)
JOHN OVENSTONE WESTWATER .....	Los Angeles, Calif.
Frederick Edward Wetzell .....	M. C., U. S. Navy
Benjamin Morrill Wheeler .....	Edmonton, Alta., Can.
CLARENCE BERNARD WHIMS .....	Atlantic City, N. J.
RANDALL ALLEN WHINNERY .....	Detroit, Mich.
Harold Nelson Willard .....	Claverack, N. Y.
Aubrey Howard Williams .....	Fort Wayne, Ind.
Conger Williams .....	Milton, Mass.
George Ralph Williamson .....	Pittsburgh, Pa.
REX HAMILTON WILSON .....	Akron, Ohio
Thomas Barnette Wilson .....	Raleigh, N. C.
IRVING WOLFE WINIK .....	Washington, D. C.
Henry John Winsauer .....	Sheboygan, Wis.
CHARLES WILMER WIRTS .....	Philadelphia, Pa.
Albert Walter Wise .....	Rock Island, Ill.
Charles Parker Wofford .....	Johnson City, Tenn.
George Anthony Wolf, Jr. ....	New York, N. Y.
RALPH WOLPAW .....	Cleveland, Ohio
John Howard Woodbridge .....	San Luis Obispo, Calif.
Thomas Clarkson Worth .....	Raleigh, N. C.
Myron Wright .....	New York, N. Y.
John Lanier Wyatt .....	Nashville, Tenn.
CARL IGLAUER WYLER .....	Cincinnati, Ohio
Hyman Joseph Zimmerman .....	Washington, D. C.
Joseph J. Zimmerman .....	Philadelphia, Pa.
Cecil M. Zukerman .....	Davenport, Iowa

### 31ST ANNUAL SESSION

#### THE AMERICAN COLLEGE OF PHYSICIANS

The Consulting Committee on Annual Sessions met with President Reginald Fitz, General Chairman Chester S. Keefer, and other representatives of the Boston Committees, on November 12, in connection with the program and arrangements for the 31st Annual Session of the College at Boston, April 17-21, 1950. With the exception of one series of panel discussions and certain hospital clinics, the scientific programs will all be conducted in Mechanics' Hall on Huntington Avenue. Several innovations, including color televised clinics, are being planned. The program of General Sessions and Morning Lectures arranged by President Fitz, and the program of Clinics and Panel Discussions, as well as entertainment features, planned by General Chairman Keefer and his local committees are fast nearing completion. A feature of entertainment will be a concert by the Boston Symphony Orchestra on Monday evening, April 17.

A Housing Bureau has been set up in connection with the Boston Convention Bureau, 80 Federal Street, Boston 10, Mass., through which all hotel reservations shall be made, except in the case of speakers on the program, Officers, Regents and Governors of the College, whose accommodations will be engaged by the Executive Secretary. An adequate number of rooms is available. A number of the functions, such as the Convocation and Annual Banquet, will be held at the Statler Hotel. Some series of the Panel Discussions will be held at the Copley Plaza Hotel. Reservation

forms for rooms will be distributed to all members with the program on or about February 1.

### *Admission of Non-Members to the Boston Meeting*

Due to excessively crowded conditions the past two years, partially occasioned by the large number of non-sponsored non-members, and at the urgent demand of members of the College, the attendance of non-members at the Boston Session will be limited to those who are specifically sponsored by letter by members of the College. Such non-members should be sponsored three weeks in advance of the Session through letters to the Executive Office of the College, 4200 Pine Street, Philadelphia 4, Pa. The non-member registration fee, which not only covers admission to the Meeting but entitles the attendant to the proceedings as published in the ANNALS OF INTERNAL MEDICINE, will be \$25.00.

---

### CANDIDATES FOR MEMBERSHIP

#### THE AMERICAN COLLEGE OF PHYSICIANS

Meetings of the Committee on Credentials will be held March 19 and April 15, 1950. Provisions of the By-Laws require that proposals of candidates shall be filed in the Executive Office at least 60 days in advance of action.

---

### PROPOSED GRADUATE COURSES

The Advisory Committee on Postgraduate Courses, with the approval of the Board of Regents, has presented the following tentative schedule of courses for the future. It must be understood that the directors and the institutions must be consulted before final announcements may be made. Furthermore, dates will be announced a little later. It is proposed to publish the Postgraduate Bulletin for the Spring of 1950 at an early date.

#### *Spring, 1950, Proposed Courses:*

INTERNAL MEDICINE: University of California School of Medicine, San Francisco; one week; to be scheduled just before the annual meeting of the American Medical Association in June, 1950.

CLINICAL ALLERGY: Roosevelt Hospital, New York, N. Y.; one week.

DISEASES OF THE CIRCULATION: Michael Reese Hospital, Chicago, Ill.; one week.

ELECTROCARDIOGRAPHY: Massachusetts General Hospital, Boston, Mass.; Conger Williams, M. D., Director; one week.

ENDOCRINOLOGY: University of Illinois et al., Chicago, Ill., Willard O. Thompson, M.D., F.A.C.P., Director; one week.

DISEASES OF THE BLOOD VESSELS: Cornell University Medical College, New York, N. Y.; one week.

PHYSIOLOGICAL BASIS OF PSYCHOSOMATIC MEDICINE: Neurological Institute, New York, N. Y.; one week.

#### *Summer, 1950, Proposed Course:*

CLINICAL ASPECTS OF MALNUTRITION: Hospital de Enfermedades de la Nutricion, Mexico, D. F.; Salvador Zubiran, M.D., F.A.C.P., Director; two weeks, August 14-26, 1950.

#### *Autumn, 1950 Proposed Courses:*

HEMATOLOGY: Boston, Mass.; William B. Castle, M.D., F.A.C.P., Director; one week.

INTERNAL MEDICINE: University of Pittsburgh School of Medicine, Pittsburgh, Pa.; R. R. Snowden, M.D., F.A.C.P., Director; one week.

GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director; one week.

INTERNAL MEDICINE: University of Utah School of Medicine, Salt Lake City, Utah; one week.

### *1951 Suggested Courses:*

INTERNAL MEDICINE WITH EMPHASIS ON PATHOLOGICAL PHYSIOLOGY: University of Cincinnati College of Medicine, Cincinnati, Ohio; M. A. Blankenhorn, M.D., F.A.C.P., Director; one week.

PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE: University of Toronto Faculty of Medicine, Toronto, Ont.; Ray F. Farquharson, M.D., F.A.C.P., Director; one week.

INTERNAL MEDICINE: University of Oregon Medical School, Portland, Ore.; Howard P. Lewis, M.D., F.A.C.P., Director; one week.

ELECTROCARDIOGRAPHY: Emory University School of Medicine, Atlanta, Ga.; R. Bruce Logue, M.D., F.A.C.P., Director; one week.

---

### LATIN-AMERICAN FELLOWSHIP PROGRAM

The American College of Physicians has announced, in the July, 1949 issue of this journal, its Latin-American Fellowship Plan in coöperation with the W. K. Kellogg Foundation. Outstanding young physicians will be nominated to the College and Foundation by local committees in Latin-American countries and those to whom fellowships are awarded will be brought to the United States or Canada for a year or more of special training. Designed to stimulate progress in the teaching of internal medicine and research, and to help the most promising young doctors of medicine in the Latin-American countries to prepare for teaching and research careers in their native countries, the program also will serve to increase understanding among the American republics by serving as a medium for the exchange of knowledge and acquaintanceships.

At a meeting of the Committee on Fellowships and Awards on July 30, 1949, the initial three Fellows were selected and were placed in an orientation course at Cornell University Medical College for a period of six months, following which they will be assigned to specific preceptors for a period of one year. These three include: Dr. Henrique BENAÏM Pinto, Caracas, Venezuela; Dr. Rudolfo DE CASTRO Curti, Mexico, D. F.; and Dr. Horacio JINICH Brook, Mexico, D. F.

Additional awards approved, to start in 1950, were made to the following: Dr. Fructuoso BIEL Cascante, Concepcion, Chile; Dr. Roberto Figueria SANTOS, Salvador, Brazil; Dr. Egon LICHTENBERGER Salomon, Bogota, Colombia; and Dr. Francisco VON LICHTENBERG Schneider, Mexico, D. F.

Dr. Benjamin G. Horning, Director of the Medical Division of the Kellogg Foundation, is responsible for the visitation and investigation of candidates in the Latin-American countries. The Committee on Fellowships and Awards of the American College of Physicians is officially responsible for the selection of the Fellows, the supervision of their program and the placing of them under a preceptor. Funds for the operation of the program are provided by the Kellogg Foundation.

---

### RESEARCH FELLOWSHIPS OF THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians awards a limited number of Fellowships in Medicine for the customary period of one year, beginning July 1 of each year. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their

preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend varies from \$2,200 to \$3,200, according to the obligations of the recipient. Application forms are obtainable through the Executive Secretary of the College, 4200 Pine Street, Philadelphia 4, Pa.

Applications may be filed for the period July 1, 1951-June 30, 1952. All Fellowships for 1950-51 have been assigned.

In accordance with the recommendations of the Committee on Fellowships and Awards, the Board of Regents on November 13, 1949, made the following awards of Research Fellowships to start July 1, 1950:

Edward Harvey Estes, Jr., M.D.; aged 24; a graduate of Emory University School of Medicine, 1947; to work under Dr. James V. Warren, Department of Physiology, Emory University School of Medicine, on the response of the pulmonary vascular bed to hemodynamic alterations in the systemic circuit.

Dalton Jenkins, M.D.; aged 31; a graduate of the University of Colorado School of Medicine, 1943; to work under Dr. George W. Thorn, F.A.C.P., Peter Bent Brigham Hospital, Boston, Mass., on a study of the adrenal hormones on specific metabolic functions, with particular relationship to muscle metabolism.

Edward Howell Lanphier, M.D.; aged 27; a graduate of the University of Illinois College of Medicine, 1949; to work under Dr. Julius H. Comroe, Jr., F.A.C.P., Department of Physiology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., on the investigation of new functional tests of the cardiovascular-pulmonary system.

William Andrew MacIlwaine, M.D.; aged 27; a graduate of the University of Virginia Department of Medicine, 1947; to work under Dr. Byrd S. Leavell, F.A.C.P., University of Virginia Department of Medicine, Charlottesville, Va., to study the effects of various procedures and substances on hemoglobin metabolism in sickle cell anemia.

Cheves McCord Smythe, M.D.; aged 25; a graduate of Harvard Medical School, 1947; to work under Dr. Stanley E. Bradley, Department of Medicine, Presbyterian Hospital, New York, N. Y., on a problem concerned with renal and hepatic physiology as studied by blood flow technics.

William Jape Taylor, M.D.; aged 25; a graduate of Harvard Medical School, 1947; to work under Dr. J. D. Myers, Department of Medicine, Duke University School of Medicine, Durham, N. C., to study the effects of insulin, epinephrine and adrenal cortical substances on the splanchnic glucose, phosphate and potassium intakes and outputs; also to study the effect of parenteral fat on hepatic blood flow and oxygen consumption.

Dr. Edward Harvey Estes, Jr. was selected from the above group of six to be designated as the "Alfred Stengel Research Fellow."

---

#### MISSISSIPPI REGIONAL MEETING REPORT

The second Annual ACP Regional Meeting of the State of Mississippi was held at Jackson, Miss., October 8, 1949, under the Governorship of Dr. John G. Archer, F.A.C.P., of Greenville. Every feature of the program and of the meeting was eminently successful, as attested to by the fact that every member of the College from Mississippi with the exception of four was present. There were 7 members of the College from Tennessee, 3 from Arkansas, and 1 from Louisiana, and among the guests were Dr. William C. Chaney, F.A.C.P., Governor for Tennessee, Dr. A. A. Blair, F.A.C.P., Governor for Arkansas, and Dr. G. W. F. Rembert, F.A.C.P., former Governor for Mississippi. At the reception and banquet in the evening, there were 71 members, guests and wives in attendance, a considerable increase over the attendance at the first Regional Meeting a year ago.



## GIFT TO THE COLLEGE LIBRARY

Grateful acknowledgment is made to Dr. Howard A. Rusk, F.A.C.P., New York, N. Y., for an autographed copy of his book, "New Hope for the Handicapped," and for several reprints dealing with rehabilitation and related subjects.

## AMERICAN COLLEGE OF PHYSICIANS ACTIVITIES IN HAWAII

Members of the American College of Physicians in Hawaii, under the leadership of Dr. Nils P. Larsen, Governor, have organized a monthly staff meeting at the Tripler General Hospital. The meetings are conducted as panel discussions with members representing different special fields discussing a chosen topic from the points of view of different medical specialties. College members will also undertake to prepare reports based on health surveys conducted in coöperation with the Board of Health. Still a further activity of the members in Hawaii includes a plan for each member to donate \$3.00 toward a subscription for the medical section of *Excerpta Medica* for the local medical library which is at present operating on a greatly curtailed budget.

## NEW BOOKS RECENTLY PUBLISHED BY FELLOWS OF THE COLLEGE

Dr. Howard T. Karsner, F.A.C.P., Washington, D. C., has recently edited "The 1948 Yearbook of Pathology and Clinical Pathology," published by the Yearbook Publishers.

Dr. Wilburt C. Davison, F.A.C.P., Professor of Pediatrics at Duke University School of Medicine, Durham, N. C., has recently brought out the 6th Edition of "The Compleat Pediatrician—Practical, Diagnostic, Therapeutic and Preventive Pediatrics," published by the Duke University Press.

Dr. Howard A. Rusk, F.A.C.P., New York, N. Y., "New Hope for the Handicapped: The Rehabilitation of the Disabled from Bed to Job," published by Harper and Brothers.

Dr. Donald C. Young (Associate) and Dr. Alvin F. Coburn, Detroit, Mich., "The Epidemiology of Hemolytic Streptococcus during World War II in the United States Navy," published by Williams and Wilkins Company.

Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn., "Obesity," published by Charles C. Thomas.

Dr. Willis M. Fowler, F.A.C.P. and Dr. Elmer L. DeGowin, F.A.C.P., Iowa City, Iowa, second edition of "Hematology for Students and Practitioners." published by Paul B. Hoeber, Inc.

## A.C.P. FELLOWS APPOINTED CONSULTANTS TO MEDICAL SERVICE, U. S. AIR FORCE

Major General Malcolm C. Grow, Surgeon General, U. S. Air Force, recently announced the appointments of Consultants to that Service, among whom are the following Fellows of the American College of Physicians: Dr. William P. Holbrook, Tucson, Ariz., and Dr. Phillip T. Knies, Columbus, Ohio, Internal Medicine; Dr. Charles E. Kossman, New York, N. Y., Cardiology; Dr. Howard A. Rusk, New York, N. Y., Physical Medicine.

## PROJECTION EQUIPMENT DONATED BY DR. LEAMAN

Dr. William G. Leaman, Jr., F.A.C.P., who directed Course No. 7, Cardiovascular Diseases, under the auspices of the American College of Physicians, at Philadelphia, Pa., May 2-7, 1949, and whose group initiated the use of the new auditorium at the College Headquarters, has donated funds to the College for the purchase of a pro-

jector for standard slides, a projector for Kodachrome slides, and a sound-motion picture 16 mm. projector. These projectors have been acquired and are of the finest quality, and are now available for all meetings or other events held at the College Headquarters. The gift was accepted with deep appreciation by the Board of Regents at its meeting on November 13, 1949.

---

#### PRESIDENT FITZ BECOMES LIFE MEMBER

Dr. Reginald Fitz, F.A.C.P., President of the American College of Physicians, became a Life Member on November 12, 1949, through a generous subscription to the Endowment Fund. The total life members number 799, of whom 69 are now deceased, leaving a balance of 730.

The Life Membership plan of the American College of Physicians is equitable both to the member and to the College. It affords the member an opportunity of paying his full dues during his productive years and while his income is greatest, and thus avoiding the burden of dues later in life. It, therefore, provides a means for underwriting dues years in advance and of receiving the premium of active membership throughout one's entire life. Members are invited to request the Executive Offices to mail them the folder, "Membership Without Dues," which gives all details.

---

#### COMING EXAMINATIONS, CERTIFYING BOARDS

(1) THE AMERICAN BOARD OF INTERNAL MEDICINE. William A. Werrell, M.D., Assistant Secretary-Treasurer, 1 West Main St., Madison, Wis. Written Examination—once yearly, to be given on 3rd Monday of October. Oral Examination—Chicago, Ill., February 8-9-10, 1950; Boston, Mass., April 13-14-15, 1950; San Francisco, Calif., June 21-22, 23, 1950.

The examination in Boston is given during the week just preceding the Annual Session of the American College of Physicians; the examination in San Francisco is given during the week preceding the annual meeting of the American Medical Association.

Oral examinations in the sub-specialties of Allergy, Cardiovascular Disease, Gastro-enterology and Tuberculosis will be held at the same time and places.

The closing dates for acceptance for all examinations will be January 1, 1950.

(2) THE AMERICAN BOARD OF PEDIATRICS. John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa. Written Examination—under local monitors, Thursday, January 12, 1950 from 2:00 to 4:00 p.m. This is the only written examination scheduled for 1950. Oral Examination—Richmond, Va., February 10-11-12, 1950; Philadelphia, Pa., March 31, April 1-2, 1950; San Francisco, Calif., June 23-24-25, 1950.

---

#### NATIONAL CONFERENCE ON CARDIOVASCULAR DISEASES

A National Conference on Cardiovascular Diseases will be held in Washington, D. C., January 18-20, 1950, under the joint sponsorship of the American Heart Association and the National Heart Institute of the U. S. Public Health Service. This will be the first national conference bringing together physicians, scientists, community service leaders, and members of allied professions to formulate a comprehensive program to combat the nation's leading cause of death.

Dr. Paul D. White, F.A.C.P., Chief Medical Adviser to the National Heart Institute, is Chairman of the Steering Committee.

UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL ANNOUNCES  
POSTGRADUATE COURSES, 1950

The University of California Medical School, through its Medical Extension, announces courses in various fields in 1950. Among these are the following:

CLINICAL SCIENCE AS APPLIED TO GENERAL MEDICINE: One evening session weekly for 20 weeks, January 9–May 22.

APPLIED THERAPEUTICS: January 20–February 1.

SPECIAL PROBLEMS IN PEDIATRICS: February 6–10.

FORENSIC MEDICINE: February 6–8.

GASTRO-ENTEROLOGY: August 28–30.

PSYCHIATRY AND NEUROLOGY: Designed as preparation for examinations of the American Board of Psychiatry and Neurology; August 28–November 17.

EVENING SYMPOSIA IN MEDICINE: Every Monday evening, September 18–December 4.

EMORY UNIVERSITY SCHOOL OF MEDICINE AND THE UNIVERSITY OF GEORGIA SCHOOL  
OF MEDICINE RECEIVE FEDERAL GRANTS FOR TEACHING AND  
RESEARCH IN CARDIOLOGY

Emory University School of Medicine, Atlanta, and the University of Georgia School of Medicine, Augusta, are among 85 medical schools and research institutions to which federal grants have been made for research in cardiology, including the search for a "mechanical heart," a mechanism that would replace the heart during operations. The University of Georgia School of Medicine has been allocated \$58,000 for construction and equipment and for additional laboratory and animal quarters. \$14,000 for teaching funds and \$15,120 for research goes to Emory University School of Medicine. These funds will be used to coördinate the study of heart disease. At Emory University, part of the funds will be used for x-ray equipment to take motion pictures of the heart in action.

The nationwide program for attacking heart disease is covered by federal grants totalling \$8,614,737.

ADDITIONAL FEDERAL GRANTS FOR MENTAL RESEARCH

Twelve additional federal grants have been made in aid of research in mental and emotional disorders as follows: Massachusetts General Hospital, \$26,308, prefrontal lobotomy studies; University of Iowa, \$3,915, anxiety and frustration in animal behavior; Illinois Institute of Technology, \$9,400, analysis of topical autobiographies of displaced persons; New York State Department of Mental Hygiene, \$7,000, statistical studies; New York University College of Medicine, \$21,276, childhood schizophrenia; New York University College of Medicine, \$3,726, changes in perceptual functions in organic psychoses; Columbia University, \$7,344, psychologic factors in amenorrhea; Columbia University, \$13,700, psychosomatic aspects of ulcerative colitis; Institute for Juvenile Research, Chicago, \$3,900, analysis of psychophysiology data on hypnosis and on emotional and behavior disorders; Columbia University College of Physicians and Surgeons, \$7,128, space-controlled neural lesions; Wayne University, \$19,364, cultural and psychiatric factors in mental health of Hut-terites, and University of Washington School of Medicine, \$16,262, cingulate gyrus of cerebral cortex, functions and connections.

NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD., PROPOSED \$40,000,000  
CLINICAL CENTER

A clinical center, already in course of construction, for the National Institutes of Health at Bethesda, Md., will be a combined hospital and research institution and will have elaborate medical equipment and basic science laboratories together with hospital facilities for five hundred patients. It will be a fourteen story building, air-conditioned, and will cost \$40,000,000. It is scheduled to be completed by July, 1952.

An auditorium seating 500 will be equipped with television, and some seats will be specially wired for the hard of hearing. The center will be supervised by Dr. R. E. Dyer, Director of the National Institutes of Health. It is said that the Government already has "colonies" of trainees for the center established throughout the country, who are being recruited and trained for particular types of research. Surgeon General Leonard A. Scheele of the Public Health Service states that this is to be a research center and not an institution in competition with private physicians and private hospitals. It is stated further that there will be intimate collaboration between the center and the medical schools of the country.

---

DR. J. ROSCOE MILLER, F.A.C.P., BECOMES 12TH PRESIDENT OF  
NORTHWESTERN UNIVERSITY

On October 26, 1949, Dr. J. Roscoe Miller, F.A.C.P., was installed as 12th President of Northwestern University, and was awarded the honorary degree of doctor of laws. Dr. Miller had been a member of the faculty of Northwestern University for nineteen years and had been Dean of the Medical School since 1941.

---

Dr. William B. Bean, F.A.C.P., Head of the Department of Internal Medicine at the State University of Iowa College of Medicine, Iowa City, was elected Vice President of the Central Society for Clinical Research, at its recent meeting in Chicago.

---

Dr. Theodore R. Van Dellen, F.A.C.P., Chicago, Ill., Assistant Professor of Medicine, Northwestern University Medical School, has been appointed Assistant Dean, succeeding Dr. George H. Gardner, resigned.

---

Dr. Robert F. Pitts, F.A.C.P., Syracuse, N. Y., Professor of Physiology, Syracuse University College of Medicine since 1946, has resigned to become Head of the Department of Physiology and Biophysics and Professor of Physiology at Cornell University Medical College, New York, N. Y., on January 1, 1950. Dr. Pitts was formerly on the faculty at Cornell University. He holds his Ph.D. degree from Johns Hopkins University and his M.D. from New York University. For two years, 1938-40, he was a Fellow of the Rockefeller Foundation.

---

Dr. George Morris Piersol, M.A.C.P., Secretary-General of the ACP, was a guest on the program of the Puerto Rico Medical Association Meeting at San Juan, December 14-18, 1949.

---

Dr. Harold G. Wolff, F.A.C.P., Professor of Neurology and Psychiatry, Cornell University Medical College, delivered an address on "Life Situations, Emotions and Bodily Disease" at the New School for Social Research, New York City, on November 4, 1949.

Dr. Paul D. White, F.A.C.P., Boston, Mass., delivered the annual Loevenhart Memorial Lecture, at the University of Wisconsin Medical School, Madison, Wis., November 28. The lecture is sponsored by Phi Delta Epsilon Medical Fraternity.

---

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., delivered the R. R. Huggins Memorial Lecture of the University of Pittsburgh School of Medicine on November 18, at the Mellon Institute of Pittsburgh. His subject was "Medical Ethics, Democracy and Medical Care." The lecture is sponsored by the Nu Chapter of Phi Delta Epsilon Medical Fraternity.

---

Dr. James Steele, F.A.C.P., Brooklyn, has been appointed Assistant Professor of Radiological Anatomy and Clinical Assistant Professor of Radiology at the University of South Dakota School of Medical Sciences.

---

Dr. Paul B. Magnuson, F.A.C.P., Medical Director of the Veterans Administration, in addition to being the Governor of the American College of Physicians, representing the Veterans Administration, is Secretary of the American College of Surgeons.

---

Dr. James E. Paullin, M.A.C.P., assisted by Dr. C. J. McLoughlin, F.A.C.P., both of Atlanta, is heading the Georgia Diabetes Control Drive, as a part of the national campaign to curb this disease. Support is being given by local health agencies and the Medical Association of Georgia.

---

Dr. Henry L. Bockus, F.A.C.P., Director of the Department of Internal Medicine and Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine, delivered the Julius Friedenwald Memorial Lecture of the University of Maryland, on October 27, his subject being "Acute Pancreatitis."

---

#### 170 BOARD MEN IN ARMY MEDICAL CORPS

Among the 1,457 Regular Army Officers in the Army Medical Corps as of September 30, 1949, there were 160, or just a shade under 11 per cent, who were certified by American Specialty Boards, according to figures released by the Office of the Surgeon General.

The Army is seeking additional Board men in all of the chief fields, as well as in allergy, cardiology, gastro-enterology, and pulmonary diseases. Under the Graduate Professional Training Program, the Army has residents, in both military and civilian teaching hospitals, in training for Board examinations in almost all the specialties mentioned. Also, under the Civilian Consultants Program, the Surgeon General is availing himself of the services of many civilian specialists, who assist in the teaching of the younger officers, both at home and abroad, and who otherwise contribute their skills toward the accomplishment of the mission of the Army Medical Department.

#### *Higher Pay Approved for Army Physicians*

The effect of the recently passed Career Compensation Act of 1949 on the income of medical and dental officers was analyzed today by Major General R. W. Bliss, F.A.C.P., Surgeon General of the Army. He pointed out that a physician who has completed his internship, or a graduate dentist, may be commissioned as a first lieutenant, either in the Regular Army or in the Medical or Dental Corps Reserve, and now receive total pay and emoluments amounting to \$473.88 a month (if married or

with dependents), or \$458.88 a month (if single and without dependents). These figures compare with former pay totals of \$417 and \$361, respectively.

A physician or dentist who has acquired sufficient professional experience, and who can meet the other requirements, may be commissioned directly as a captain or higher. A captain's pay, with emoluments, in the Medical and Dental Corps, is now \$546 (with dependents) or \$531 (without dependents), as against \$462 and \$426, respectively. On completion of four years of service, a captain receives regular increases at two-year intervals.

Comparable increases have been made in the higher grades, thus making the financial rewards of military service more commensurate with those of private practice.

---

The Institute for Cancer Research and the Lankenau Hospital Research Institute, Philadelphia, held opening exercises for its new laboratories in Fox Chase on November 16, 1949. There was a program covering a discussion on "Modes of Procedure in Cancer Research," followed by "Open House" and demonstrations by the staffs of the Institutes.

The new laboratories are extensive and represent in facilities and equipment the finest possible setup for cancer research. The staff is being enlarged materially. Both Institutes were organized and have been directed for many years by Dr. Stanley Reimann, F.A.C.P.

---

The Southern Medical Association held its forty-third Annual Meeting in Cincinnati, Ohio, November 14-17, 1949, under the presidency of Dr. Oscar B. Hunter F.A.C.P., Washington, D. C.

---

#### ANOTHER POST-CONVENTION CRUISE TO BERMUDA, FOLLOWING THE BOSTON SESSION, 1950

Following the Annual Session of the American College of Physicians at New York during the Spring of 1949, an official cruise was conducted to Bermuda, occupying a period of approximately one week. Those of the College who went on the cruise were delighted with all the arrangements and the beauties of the islands. Many were disappointed who could not accompany the group.

The Annual Session in Boston comes at a time, April 17-21, 1950, when there are no appropriate post-convention tours available in the New England states, due to the uncertainty of weather and other factors. Consequently, it has been decided to offer again the cruise to Bermuda. Members can take a late afternoon or evening train from Boston on Friday, April 21, arriving in New York, Saturday morning, where they may spend their morning on personal affairs, and board the "Queen of Bermuda" in the early afternoon. The Itinerary is as follows:

- April 22, Sat., 3:00 p.m. Sail from New York; The famous Bays and Skyline, Tea, Dancing in the evening.
- 23, At sea, the Gulf Stream, Movies, Tea, Dancing.
- 24, Bermuda, the beautiful islands. Cruise along the charming North Shore and into Hamilton Harbor, one of the loveliest in the world. Arrive Hamilton at 9 a.m.
- 25, About two and a half days in Bermuda. Opportunity for unusual sight-seeing drives, visits to the Caves and Coral Gardens, shopping, golf, or other diversions.
- 26, Plenty of time today for last minute purchases or drives. Leave Hamilton at 3:00 p.m.

27, Again at sea in the Gulf Stream, Movies, Tea, Dancing.

28, 9:00 a.m. Arrive New York. In most cases members living East of the Mississippi may keep office appointments on Saturday.

The cruise ship will be the luxurious "Queen of Bermuda", especially designed on a world-cruise pattern for the Bermuda run. Every room has a private bath as well as forced ventilation directly under the control of the passengers in each room. The spacious lounges and cafes, swimming pool, ball room, and cozy nooks give the "Queen" the atmosphere of an exclusive club.

The Hotel Princess, a distinguished hostelry in Bermuda, overlooking Hamilton Harbor and the landscaped hills beyond, will be headquarters.

The inclusive price ranges from a minimum of \$184.30 up, depending on the type of accommodations demanded.

For full information, plan of the ship, rates, and other data, write direct to Leon V. Arnold, 36 Washington Square West, New York 11, N. Y., who is the conductor of the cruise and who has served the College on previous occasions.

## OBITUARIES

## DR. THOMAS ADDIS

Thomas Addis, M.D., F.R.C.P., F.A.C.P., San Francisco, Calif., died June 4, 1949, at the age of 67. Dr. Addis was born in Scotland, July 27, 1881. He received the degree of M.B., Ch.B. in 1905, from the University of Edinburgh Faculty of Medicine, and thereafter pursued postgraduate work for two years at Berlin and Heidelberg, Germany. He joined the faculty of Stanford University School of Medicine in 1911, and became Professor of Medicine, serving until 1946, when he retired from active teaching. He was a Fellow of the Royal College of Physicians of Edinburgh and received from that organization, in 1942, the Cullen Prize "for the greatest benefit done to practical medicine in the previous four years." He was a member of the Association of American Physicians, National Academy of Sciences, the American Society for Clinical Investigation, and had been a Fellow of the American College of Physicians since 1930. He was also a diplomate of the American Board of Internal Medicine.

Dr. Addis was a former Carnegie Research Scholar and Fellow, and the first Visiting Fellow at the Long Island College of Medicine, Brooklyn. He had many publications to his credit, among which were "Renal Lesion in Bright's Disease" and "Glomerular Nephritis: Diagnosis and Treatment."

## DR. WILLIAM DUNCAN REID

Dr. William Duncan Reid, F.A.C.P., of North Parsonfield, Maine, was a resident of Massachusetts for many years before his retirement. He graduated from Harvard Medical School in 1909 and during World War I served with the American Expeditionary Forces in France. During all the years of his medical life, Dr. Reid was interested in heart disease, and two books appeared under his authorship, "The Heart in Modern Practice" and "Teaching Methods in Medicine." When the first electrocardiograph machine was installed in the Boston City Hospital, Dr. Reid supervised this important department and emphasized the physiological approach to the study and understanding of heart disease. For many years, his interest in the heart during pregnancy commanded his attention and study. All of his friends profited by associating with him, and his students were admiring and loyal.

CHESTER S. KEEFER, M.D., F.A.C.P.,

Governor for Massachusetts

## DR. BRUCE HUTCHINSON DOUGLAS

Bruce Hutchinson Douglas, A.B., M.D., F.A.C.P., Detroit, Mich., was instantly killed in an automobile accident, en route on a much needed vacation, on August 11, 1949.

Dr. Douglas was born on August 26, 1892. He graduated, A.B., 1915, from Whittier College, and M.D., 1921, from the Rush Medical School. Following graduation he served an internship and residency in the Children's Hospital and in the Herman Kiefer Hospital, Detroit. During 1924-25 he carried on postgraduate studies in preventive medicine and tuberculosis in England, Denmark and Switzerland. Following graduation and residency, Dr. Douglas devoted his life to preventive medicine and to work in the field of tuberculosis. In these fields he became an outstanding authority and teacher. For two years, 1923-25, he was a Lecturer on Tuberculosis to the undergraduate students in the University of Michigan Medical School. Later he became a Lecturer on Tuberculosis in the University of Michigan Postgraduate School of Medicine. For many years he taught preventive medicine and public health in the Wayne University College of Medicine, and in 1941 he became Professor of



Preventive Medicine and Public Health. During the 1930's he served as Medical Director of the Tuberculosis Service at the Herman Kiefer Hospital and Consultant to the William H. Maybury Sanatorium. Later he became Controller of Tuberculosis for the Detroit Department of Health. In 1941 he was elevated to Commissioner of Health in the Detroit Department of Health. In this capacity he served until his unfortunate and untimely death.

Dr. Douglas was a man of great scientific achievements in his field of preventive medicine. He had an amazing capacity for friendship and an ability to get along with his fellow physicians. For this reason the Detroit Department of Health became outstanding throughout the country. Private physicians admired and trusted him. Nowhere else in the country has there been built up such splendid coöperation between the public health service and the private practitioner.

DOUGLAS DONALD, M.D., F.A.C.P.,  
Governor for Michigan

### DR. HILLYER RUDISILL, JR.

Dr. Hillyer Rudisill, Jr., a Fellow of the American College of Physicians for many years, died suddenly of coronary thrombosis at his home on the morning of July 27, 1949.

Dr. Rudisill was born in Macon, Georgia, February 28, 1902. After his undergraduate work at Mercer University, for which he received a B.S. degree, he was graduated from the Jefferson Medical College of Philadelphia in 1924. After visiting hospitals and clinics abroad he interned in New York City and later completed post-graduate work in the field of radiology at the University of Chicago. In 1931 he resigned as Instructor in Roentgenology at the University of Chicago and moved to Charleston, S. C., where he became Professor of Radiology and Radiologist at the Roper Hospital. In 1939 he moved to Atlanta and was Director of the Radiological Department of the Piedmont Hospital, and in 1941 he became Assistant Professor of Radiology at the University of Tennessee College of Medicine and Radiologist to the John Gaston Hospital. He returned to Charleston in 1944, reassuming the duties of Radiologist at the Roper Hospital and continued in this capacity until some months before his death when he attained a long-held ambition and entered the private practice of Radiology. Throughout this time he maintained his teaching connection with the Medical College of South Carolina.

Dr. Rudisill was a member of the Medical Society of South Carolina, of the South Carolina State Medical Association, of the American Roentgen Ray Society, of the American Rheumatism Association, of the Southern Medical Association, and he was a Fellow of the American College of Radiology and of the American College of Physicians. He was also a Diplomate of the American Board of Radiologists.

Dr. Rudisill brought to his chosen field an ingenious and original mind aware both of the possibilities and limitations of radiology. He improvised a device for use in foreign body localization and a probe for seeking metallic particles in subcutaneous tissues. He was the author of a number of scientific publications on both technical and therapeutic subjects, including a manual for x-ray technicians, and contributed to the Official Navy X-Ray Reference Work with a chapter on foreign body localization.

Aside from his professional attainments Dr. Rudisill's interests were wide and varied. He collected a number of items and at one time established an x-ray museum. He was an enthusiastic member of a local Medical History Club and his contributions were always interesting and original. He combined an attractive personality with a keenly analytic mind and an inquisitive nature and was a constant force in compelling both his students and his colleagues to the ultimate in scientific exactitude.

ROBERT WILSON, JR., M.D., F.A.C.P.,  
Governor for South Carolina

## DR. W. HUARD HARGIS, JR.

Dr. W. Huard Hargis, Jr., died of poliomyelitis on August 15, 1949, in San Antonio, Texas, where he was born on December 27, 1912. Dr. Hargis was a graduate of the University of Texas School of Medicine and received the degrees of B.S. in Medicine and M.D. in 1936. He served an internship at the University of Iowa Hospital in 1936-37, and was a Fellow in Internal Medicine of the Mayo Foundation and received the degree of Master of Science in Medicine in 1942. During World War II, Dr. Hargis was a Major in the Medical Corps of the United States Army.

He was Chief of the Medical Service of the Robert B. Green Memorial Hospital, San Antonio, and Director of the Clinic of the Baptist Memorial Hospital, San Antonio. Dr. Hargis was a Diplomate of the American Board of Internal Medicine and a member of the Bexar County Medical Society, Texas State Medical Association and the American Medical Association. He has been an Associate of the American College of Physicians since 1945. In February of 1948, Dr. Hargis was elected a member of the Texas Club of Internists. He was held in high esteem by his colleagues and a most promising career was closed by his untimely death.

D. W. CARTER, JR., M.D., F.A.C.P.,  
Governor for Texas

## DR. FREDERIC A. ALLING

Dr. Frederic A. Alling died, aged 65, at his home in Montclair, N. J., on October 20, 1949. He had been ill for several months with a malignant hypertension.

He lived a life of intense activity. Always hard working and devoted to his profession, his patients and friends were devoted to him. He became one of the leading and most respected internists in the state.

He was graduated from Princeton in 1907 and from the College of Physicians and Surgeons, Columbia University, in 1911. He interned at the New York Hospital, began practice in Newark, and married Helen, daughter of Bishop Stearley. She and two sons and two daughters survive him.

In World War I Dr. Alling served overseas with the New York Hospital Unit with the rank of Captain. He was an Attending Physician at Newark City Hospital, St. Barnabas Hospital and Presbyterian Hospital, all of Newark. At St. Barnabas he had been President of the Medical Staff. He was Consulting Physician at Rahway and Newark Memorial Hospitals, the Newark Eye and Ear Infirmary, and the Essex Mountain Sanitorium. He was a former president of the Practitioners Society, and had taken an active part in the Essex County and New Jersey State Medical Societies as well as the Academy of Medicine of Northern New Jersey. He was made a Fellow of the College in 1938.

A man of great capacity and many interests, Dr. Alling will be sorely missed by patients, friends, and associates.

GEORGE H. LATHROPE, M.D., F.A.C.P.,  
Governor for New Jersey

## DR. JOHN WALTER TORBETT

Dr. J. W. Torbett, F.A.C.P., of Marlin, Texas, died on August 9, 1949, of coronary occlusion.

Dr. Torbett was born July 12, 1871, near Jacksonville, Texas. He was graduated a Bachelor of Science from Centenary College, Lampasas, Texas, in 1891, and received his medical degree from the Atlanta Medical College, Atlanta, Georgia, in 1895, graduating with highest honors. Dr. Torbett practiced continuously in Marlin, Texas, from 1896 until the time of his death. Here he established a clinic and hos-

pital, taking advantage of local mineral waters to create what became a nationally recognized health resort.

Dr. Torbett was a member of the Texas State Medical Association and of the American Medical Association throughout his career. He was Vice-President of the Texas State Medical Association in 1923-24 and 1931-32, and chairman of the Section on Gynecology and Obstetrics in 1919, and chairman of the Section on Radiology and Physical Medicine in 1926. He was president of the Falls County Medical Society in 1947 and also served as president of the Twelfth District Medical Society. He was a diplomate of the American Board of Internal Medicine and of the American Board of Physical Medicine and a life member and a Fellow of the American College of Physicians. He was also a member of the American Congress on Physical Medicine.

Dr. Torbett was a man of unusual talents. He wrote several booklets of poetry and was an accomplished violinist. Philanthropic interests were manifested by scholarships which he established at Southern Methodist University, Dallas, and Southwestern University, Georgetown, Texas, and by many years of public service as a public school trustee, as chairman of the Board of Trustees of the Methodist Orphans' Home of Waco, Texas, and as chairman of the board of stewards of his church.

In 1930 the honorary degree of doctor of laws was conferred upon Dr. Torbett by Southern Methodist University, of which institution he was a founder. His autobiography entitled, "The Doctor's Scrapbook," was published a few years ago.

He was held in high esteem and deep affection by his professional colleagues, patients and many friends.

DAVID W. CARTER, JR., M.D., F.A.C.P.,  
Governor for Texas

#### DR. WILLIAM HENRY CADE

Dr. William H. Cade of San Antonio, Texas, died July 4, 1949, in San Antonio of coronary occlusion. He was born in San Antonio on November 6, 1892, and received his preliminary education at the University of Texas and was graduated from the University of Texas School of Medicine in May, 1916. From December, 1916, until July, 1917, Dr. Cade practiced in Schertz, Texas. He was a lieutenant in the United States Army from July, 1917, to February, 1919, serving in France. Upon his return from Army service in 1919, Dr. Cade practiced continuously in San Antonio until his death.

Dr. Cade was a member of the Bexar County Medical Society, of which he was president in 1937. He belonged to the State Medical Association of Texas and served as chairman of the Section on Medicine and Diseases of Children in 1936. He was a fellow of the American Medical Association and a member of the International Post-graduate Medical Assembly of Southwest Texas. Of the latter organization he was president in 1935. He was elected a Fellow of the American College of Physicians in 1940. Dr. Cade was a member of staffs of Santa Rosa, Nix and Robert B. Green Hospitals of San Antonio.

He was held in high esteem by his colleagues and patients.

D. W. CARTER, JR., M.D., F.A.C.P.,  
Governor for Texas

# ANNALS OF INTERNAL MEDICINE

## AUTHOR INDEX

Volume 31, July-December, 1949

- ANGRIST, A., E. D. ROBBINS and —. Necrosis of the renal papillae. . . . . 773
- APPLEBAUM, E. and S. M. ARONSON. Erythema multiforme bullosum due to sulfadiazine sensitivity controlled with procaine intravenously. *Case Rep.* . . . . . 146
- ARANOW, H., JR., G. F. CAHILL and —. Pheochromocytoma: diagnosis and treatment. . . . . 389
- ARONSON, S. M., E. APPLEBAUM and —. Erythema multiforme bullosum due to sulfadiazine sensitivity controlled with procaine intravenously. *Case Rep.* . . . . . 146
- BARRETT, R. H. Sodium succinate— an analeptic for barbiturate poisoning in man. . . . . 739
- BAYNE-JONES, S. The hospital as a center of preventive medicine. . . . . 7
- BEAKEY, J. F., E. A. GAENSLER, —and M. S. SEGAL. Pharmacodynamics of pulmonary absorption in man. I. Aerosol and intratracheal penicillin. . . . . 582
- BEAKEY, J. F., E. A. GAENSLER and M. S. SEGAL. Pharmacodynamics of pulmonary absorption in man. II. The influence of various diluents on aerosol and intratracheal penicillin. . . . . 805
- BERGMAN, H. C., M. PRINZMETAL, L. L. SCHWARTZ, E. CORDAY, R. SPRITZLER, —and H. E. KRUGER. Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion. . . . . 429
- BICKERMAN, L. J. and E. E. IRONS. Myocardial infarction resulting in interventricular septal perforation; report of case diagnosed during life. *Case Rep.* . . . . . 918
- BOAS, E. P. and N. F. BOAS. Coronary artery disease. *Rev.* . . . . . 360
- BOCKUS, H. L., T. S. SAPPINGTON and —. Nitrogen balance studies in chronic peptic ulcer disease. . . . . 271
- Nitrogen metabolism in chronic idiopathic ulcerative colitis and its therapeutic significance. . . . . 282
- BOONE, B. R., G. F. ELLINGER and F. G. GILICK. Electrocardiography of the heart and great vessels: principles and application. . . . . 1030
- BOONE, J. A. and H. G. SMITHY. Vena caval thrombosis with polycythemia and leg ulcer. *Case Rep.* . . . . . 513
- BOUCOT, K. R., D. A. COOPER, E. W. MARSHALL and F. MACD. RICHARDSON. Chest x-ray surveys in general hospitals, a critical review. . . . . 889
- BURCH, G. E. and C. T. RAY. Lower nephron syndrome. . . . . 750
- BURCH, G. E. and T. WINSOR. A primer of electrocardiography. *Rev.* . . . . 171
- CAHILL, G. F. and H. ARANOW, JR. Pheochromocytoma: diagnosis and treatment. . . . . 389
- CANTAROW, A. and M. TRUMPER. Clinical biochemistry. *Rev.* . . . . . 934
- CAPLAN, P. S., H. M. MARGOLIS and —. The use of curare (d-tubocurarine in oil and wax) in the treatment of muscle spasm in rheumatic disorders. . . . . 615
- CHURG, J., N. UHR and —. Hypertrophic osteoarthropathy; report of a case associated with a chordoma of the base of the skull and lymphangitic pulmonary metastases. *Case Rep.* . . . . 681
- CHUSID, J. G., J. J. McDONALD, —and J. LANGE. Correlative neuroanatomy. *Rev.* . . . . . 704
- CLARK, E., L. WALLACE and —. Electrocardiographic changes in a case of Wernicke's syndrome. *Case Rep.* . . . . 675
- COLLINS, H. S., M. FINLAND, —T. M. GOCKE and E. B. WELLS. Present status of aureomycin therapy. . . . . 39
- COMROE, B. I. Arthritis and allied conditions. *Rev.* . . . . . 932

- CONYBEARE, JOHN, Editor. Textbook of medicine. *Rev.*..... 932
- COOKE, R. A. The allergy factor in disease..... 17
- COOPER, D. A., K. R. BOUCOT,—E. W. MARSHALL and F. MACD. RICHARDSON. Chest x-ray surveys in general hospitals, a critical review..... 889
- CORDAY, E., M. PRINZMETAL, L. L. SCHWARTZ,—R. SPRITZLER, H. C. BERGMAN and H. E. KRUGER. Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion..... 429
- CORDAY, E., R. SPRITZLER and M. PRINZMETAL. Studies on the coronary circulation. VII. The remarkable reserve power of the heart..... 450
- CREHAN, E. L., E. R. H. KURZ,—and C. THOMSON. Salmonella endocarditis with streptomycin failure. *Case Rep.* 497
- CROHN, B. B. Regional ileitis. *Rev.* 529
- CURRENS, J. H. and P. D. WHITE. Great reduction in heart size attending the clearing of congestive heart failure in a man with hypertensive and coronary heart disease. *Case Rep.* 912
- DAHLLIN, D. C. Secondary amyloidosis 105
- DOAN, C. A. The etiology and management of the hemorrhagic diatheses.. 967
- DOMZALSKI, C. A., JR. Calcareous pancreatitis..... 650
- DRESSLER, W. and H. ROESLER. An atlas of electrocardiography. *Rev.* 933
- DWYER, C. S., S. KRONENBERG and M. SAKLAD. Anginal syndrome during sodium succinate therapy. *Case Rep.* 148
- EDELMAN, I. S. Paraplegia secondary to metastatic carcinoma treated with stilbestrol. *Case Rep.*..... 1098
- EDWARDS, E. A. Phlebitis and the diagnosis of thromboangiitis obliterans..... 1019
- ELLINGER, G. F., B. R. BOONE,—and F. G. GILICK. Elektokymography of the heart and great vessels: principles and application..... 1030
- ENGLISH, O., E. WEISS and—. Psychosomatic medicine: the clinical application of psychopathology to general medical problems. *Rev.*..... 532
- EVANS, W. Cardiology. *Rev.*..... 172
- FEDER, A. Clinical observations on atypical lichen planus and related dermatoses presumably due to atabrine toxicity..... 1078
- FEDER, I. A., N. MITCHELL and—. Kaposi's sarcoma with secondary involvement of the jejunum, perforation and peritonitis. *Case Rep.* 324
- FERRERO, C., P. D. WHITE and—. Research problems in coronary heart disease..... 33
- FINLAND, M., H. S. COLLINS, T. M. GOCKE and E. B. WELLS. Present status of aureomycin therapy..... 39
- FISCHL, A. A. and J. PAPPS. Diagnostic features of splenic cysts with case report and review of the literature. *Case Rep.*..... 1105
- FORSQREN, A. L. A case of a putrid empyema with a bronchopleural fistula successfully treated with penicillin. *Case Rep.*..... 691
- FOX, T. T. On the significance of the normal electrocardiogram in old age.. 120
- FREIMUTH, H. C., D. GROB, W. L. GARLICK, G. G. MERRILL and—. Death due to parathion, an anticholinesterase insecticide. *Case Rep.*.... 899
- FRIEDMAN, A. J., M. B. SIEGEL and—. Fatal mercurialism due to prolonged intravenous administration of a mercurial diuretic. *Case Rep.*..... 343.
- GAENSLER, E. A., J. F. BEAKEY and M. S. SEGAL. Pharmacodynamics of pulmonary absorption in man. I. Aerosol and intratracheal penicillin.. 582
- GAENSLER, E. A., J. F. BEAKEY,—and M. S. SEGAL. Pharmacodynamics of pulmonary absorption in man. II. The influence of various diluents on aerosol and intratracheal penicillin... 805
- GARDNER, F. E. and P. D. WHITE. Coronary occlusion and myocardial infarction associated with chronic rheumatic heart disease..... 1003
- GARLICK, W. L., D. GROB,—G. G. MERRILL and H. C. FREIMUTH. Death due to parathion, an anticholinesterase insecticide. *Case Rep.*.... 899
- GILICK, F. G., B. R. BOONE, G. F. ELLINGER and—. Elektokymography of the heart and great vessels: principles and application..... 1030

- GLASS, W. H. Persistent tachycardia caused by snake venom. *Case Rep.*... 517
- GOCKE, T. M., M. FINLAND, H. S. COLLINS,—and E. B. WELLS. Present status of aureomycin therapy.... 39
- GOLD, M. M. A., K. LANGE, D. WEINER and—. Studies on the mechanism of cardiac injury in experimental hypothermia..... 989
- GOLDMAN, A. M. and J. D. RIVES. A case of mesenteric venous thrombosis with survival. *Case Rep.*..... 329
- GREEN, M. A. Aerosol penicillin in allergic patients with respiratory infections..... 260
- GROB, D., W. L. GARLICK, G. G. MERRILL and H. C. FREIMUTH. Death due to parathion, an anticholinesterase insecticide. *Case Rep.*..... 899
- GRUSKIN, B. J. Aureomycin in acute infectious mononucleosis. *Case Rep.* 678
- GUTTENTAG, O. E. On the clinical entity..... 484
- HAMILTON, K. A. Pulmonary disease manifestations of ankylosing spondylarthritis..... 216
- HARRIS, N. G., Editor. Modern trends in psychological medicine. *Rev.*.... 171
- HARTZ, A. S. The diagnosis of pneumonia preceding tuberculosis..... 1066
- HARVEY, W. P., S. A. LEVINE and—. Clinical auscultation of the heart. *Rev.*..... 704
- HAYES, E. W., Editor. The fundamentals of pulmonary tuberculosis and its complications, for the student, the teacher, and the practicing physician. *Rev.*..... 532
- HERSH, A. H., R. M. STECHER,—and W. M. SOLOMON. The heredity of gout and its relationship to familial hyperuricemia..... 595
- HILKER, A. W. The shoulder-hand syndrome: a complication of coronary artery disease..... 303
- IRONS, E. E., L. J. BICKERMAN and—. Myocardial infarction resulting in interventricular septal perforation: report of a case diagnosed during life. *Case Rep.*..... 918
- JONES, C. C., P. H. MORTON and—. Tropical eosinophilia with report of a case treated with penicillin. *Case Rep.*..... 1112
- KANNER, L. Child psychiatry. *Rev.*... 362
- KARPMAN, B. Case studies in the psychopathology of crime. *Rev.*..... 170
- KEMPNER, W. Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet..... 821
- KLEINER, I. S. Human biochemistry. *Rev.*..... 1134
- KONORSKI, J. Conditioned reflexes and neuron organization. *Rev.*..... 1133
- KRONENBERG, S., C. S. DWYER,—and M. SAKLAD. Anginal syndrome during sodium succinate therapy. *Case Rep.*..... 148
- KRUGER, H. E., M. PRINZMETAL, L. L. SCHWARTZ, E. CORDAY, R. SPRITZLER, H. C. BERGMAN and—. Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion..... 429
- KURZ, E. R. H., E. L. CREHAN and C. THOMSON. Salmonella endocarditis with streptomycin failure. *Case Rep.* 497
- LANGE, J., J. J. McDONALD, J. C. CHUSID and—. Correlative neuroanatomy. *Rev.*..... 704
- LANGE, K., D. WEINER and M. M. A. GOLD. Studies on the mechanism of cardiac injury in experimental hypothermia..... 989
- LEVINE, S. A. and W. P. HARVEY. Clinical auscultation of the heart. *Rev.*..... 704
- LICHTMAN, S. S. Diseases of the liver, gallbladder, and bile ducts. *Rev.*.... 531
- LINTON, R. R. The surgical treatment of bleeding esophageal varices by portal systemic venous shunts with a report of 34 cases..... 794
- LONGCOPE, W. T. and J. A. LUETSCHER, JR. The use of BAL (British Anti-Lewisite) in the treatment of the injurious effects of arsenic, mercury and other metallic poisons..... 545
- LOWEN, H. J. and H. E. B. PARDEE. Unipolar extremity leads in records with large Q<sub>3</sub>..... 456

- LUETSCHER, J. A., JR., W. T. LONGCOPE and—. The use of BAL (British Anti-Lewisite) in the treatment of the injurious effects of arsenic, mercury and other metallic poisons. . . . 545
- LUISADA, A. A. Heart: a physiologic and clinical study of cardiovascular diseases. *Rev.* . . . . . 1133
- MANN, N., I. ZIMMERMAN and—. Boeck's sarcoid: a case of sarcoidosis complicated by pulmonary emphysema and cor pulmonale. *Case Rep.* . . . . . 153
- MARGOLIS, H. M. and P. S. CAPLAN. The use of curare (d-tubocurarine in oil and wax) in the treatment of muscle spasm in rheumatic disorders. . . . . 615
- MARSHALL, E. W., K. R. BOUCOT, D. A. COOPER,—and F. MACD. RICHARDSON. Chest x-ray surveys in general hospitals, a critical review. . . . . 889
- MCCOMBS, R. P. Newer concepts of medical care. . . . . 125
- MCDONALD, J. J., J. G. CHUSID and J. LANGE. Correlative neuroanatomy. *Rev.* . . . . . 704
- MEISTER, L., D. NIEMETZ, A. SOKOL and —. Polycystic disease of the liver; report of two cases diagnosed by peritoneoscopy. *Case Rep.* . . . . . 319
- MELAMED, M. and A. MELAMED. Prolapsed gastric mucosa: a possible cause of "gastric" symptoms in right heart failure. . . . . 245
- MENNINGER, W. C. Emotional factors in organic disease. . . . . 207
- MERRILL, G. G., D. GROB, W. L. GARLICK,—and H. C. FREIMUTH. Death due to parathion, an anticholinesterase insecticide. *Case Rep.* . . . . . 899
- MEYN, W. P., L. SCHWAB, G. L. SMILEY and—. Xiphosternal crunch: an analysis of 106 cases among 3,224 army separatees. . . . . 228
- MIDDLETON, W. S. Streptomycin therapy of *Hemophilus influenzae* endocarditis lenta. *Case Rep.* . . . . . 511
- MITCHELL, D. C., R. W. VILTER and C. F. VILTER. Hypersensitivity to folic acid. *Case Rep.* . . . . . 1102
- MITCHELL, N. and I. A. FEDER. Kaposi's sarcoma with secondary involvement of the jejunum, perforation and peritonitis. *Case Rep.* . . . . . 324
- MORTON, P. H. and C. C. JONES. Tropical eosinophilia with report of a case treated with penicillin. *Case Rep.* . . . . . 1112
- MOURAO, M. M. and R. SCHINDLER. Pancreatic lithiasis and gastritis (cases with gastroscopic observations) . . . . . 83
- MUDD, S. Electron microscopy in relation to the medical sciences. . . . . 570
- NEEFE, J. R. Viral hepatitis: problems and progress. . . . . 857
- NEUDA, P. M. Red blood cell sensitivity in Caucasians. . . . . 1024
- NIEMETZ, D., A. SOKOL and L. MEISTER. Polycystic disease of the liver; report of two cases diagnosed by peritoneoscopy. *Case Rep.* . . . . . 319
- PACKER, H. and Y. T. WONG. Penicillin and penicillin-malaria in the treatment of tabes dorsalis. . . . . 96
- PALMER, W. W. The internist, past, present, and future. . . . . 1
- PAPANICOLAOU, G. N. A survey of the actualities and potentialities of exfoliative cytology in cancer diagnosis. . . . . 661
- PAPPS, J., A. A. FISCHL and—. Diagnostic features of splenic cysts with case report and review of the literature. *Case Rep.* . . . . . 1105
- PARDEE, H. E. B., H. J. LOWEN and —. Unipolar extremity leads in records with large Q<sub>3</sub>. . . . . 456
- PEPPER, O. H. P. Medical etymology, the history and derivation of medical terms for students of medicine, dentistry and nursing. *Rev.* . . . . . 530
- PINCUS, G. and K. V. THIMANN, Editors. The hormones: physiology, chemistry, and applications. *Rev.* . . . . 169
- POOL, J. L. Prefrontal operations for the treatment of mental illness. . . . . 424
- PRICE, D. S. Tuberculosis in childhood. *Rev.* . . . . . 171
- PRINZMETAL, M., L. L. SCHWARTZ, E. CORDAY, R. SPRITZLER, H. C. BERGMAN and H. E. KRUGER. Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion. . . . . 429

- PRINZMETAL, M., E. CORDAY, R. SPRITZLER and—. Studies on the coronary circulation. VII. The remarkable reserve power of the heart. . . 450
- RAISBECK, M. J., S. A. THOMPSON and—. The surgical rehabilitation of the coronary cripple. . . . . 1010
- RAY, C. T., G. E. BURCH and—. Lower nephron syndrome. . . . . 750
- REES, J. R., Editor. Modern practice in psychological medicine. *Rev.*. . . 1133
- RENNER, W. F. Pulmonary embolism with acute cor pulmonale and extremely rapid ventricular rate in a young, active, apparently healthy adult. *Case Rep.*. . . . . 1090
- RICE, M. L., JR., C. E. THOMPSON and—. Secondary amyloidosis in spinal cord injury. . . . . 1057
- RICHARDSON, F. MACD., K. R. BOUCOT, D. A. COOPER, E. W. MARSHALL and—. Chest x-ray surveys in general hospitals, a critical review. . . . . 889
- RIVES, J. D., A. M. GOLDMAN and—. A case of mesenteric venous thrombosis with survival. *Case Rep.*. . . . 329
- ROBBINS, E. D. and A. ANGRIST. Necrosis of renal papillae. . . . . 773
- ROESLER, H., W. DRESSLER and—. An atlas of electrocardiography. *Rev.*. . . . . 933
- ROSE, H. M. The clinical manifestations and laboratory diagnosis of rickettsialpox. . . . . 871
- ROSENBLATT, P., S. D. SPATT and—. The incidence of hypertension in portal cirrhosis: a study of 80 necropsied cases of portal cirrhosis. . . . . 479
- ROSENBLOOM, S. E. Superior vena cava obstruction in primary cancer of the lung. . . . . 470
- ROSENBLUM, A. H. Typhoid and paratyphoid fever in immunized subjects. . . 235
- ROSENTHAL, N., J. M. SPITZER,—M. WEINER and S. SHAPIRO. Pulmonary embolism: its incidence at necropsy in relation to peripheral thrombosis. . . . . 884
- SAGLAD, M., C. S. DWYER, S. KRONENBERG and—. Anginal syndrome during sodium succinate therapy. *Case Rep.*. . . . . 148
- SAPPINGTON, T. S. and H. L. BOCKUS. Nitrogen balance studies in chronic peptic ulcer disease. . . . . 271
- Nitrogen metabolism in chronic idiopathic ulcerative colitis and its therapeutic significance. . . . . 282
- SCHINDLER, R., M. M. MOURAO and—. Pancreatic lithiasis and gastritis (cases with gastroscopic observations). . . . . 83
- SCHWAB, L., G. L. SMILEY and W. P. MEYN. Xiphosternal crunch: an analysis of 106 cases among 3,224 army separatees. . . . . 228
- SCHWARTZ, L. L., M. PRINZMETAL,—E. CORDAY, R. SPRITZLER, H. C. BERGMAN and H. E. KRUGER. Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion. . . . . 429
- SEABURY, J. H. Stilbamidine in the treatment of histoplasmosis. *Case Rep.*. . . . . 520
- SEGAL, M. S., E. A. GAENSLER, J. F. BEAKEY and—. Pharmacodynamics of pulmonary absorption in man. I. Aerosol and intratracheal penicillin. . . 582
- SEGAL, M. S., J. F. BEAKEY, E. A. GAENSLER and—. Pharmacodynamics of pulmonary absorption in man. II. The influence of various diluents on aerosol and intratracheal penicillin. . . . . 805
- SHAPIRO, S., J. M. SPITZER, N. ROSENTHAL, M. WEINER and—. Pulmonary embolism: its incidence at necropsy in relation to peripheral thrombosis. . . . . 884
- SIEGEL, M. B. and A. J. FRIEDMAN. Fatal mercurialism due to prolonged intravenous administration of a mercurial diuretic. *Case Rep.*. . . . . 343
- SIGLER, L. Cardiovascular disease. *Rev.*. . . . . 934
- SMILEY, G. L., L. SCHWAB,—and W. P. MEYN. Xiphosternal crunch: an analysis of 106 cases among 3,224 army separatees. . . . . 228
- SMITH, D. T. Immunologic types of blastomycosis: a report on 40 cases. . . 463
- SMITH, J. G. The electrocardiographic syndrome following paroxysmal tachycardia. *Case Rep.*. . . . . 504



- SMITHY, H. G., J. A. BOONE and—. Vena caval thrombosis with polycythemia and leg ulcer. *Case Rep.*.... 513
- SNYDER, F. F. Obstetric analgesia and anesthesia. *Rev.*..... 705
- SOKOL, A., D. NIEMETZ,—and L. MEISTER. Polycystic disease of the liver; report of two cases diagnosed by peritoneoscopy. *Case Rep.*..... 319
- SOLOMON, W. M., R. M. STECHER, A. H. HERSH and—. The heredity of gout and its relationship to familial hyperuricemia..... 595
- SPATT, S. D. and P. ROSENBLATT. The incidence of hypertension in portal cirrhosis: a study of 80 necropsied cases of portal cirrhosis..... 479
- SPITZER, J. M., N. ROSENTHAL, M. WEINER and S. SHAPIRO. Pulmonary embolism: its incidence at necropsy in relation to peripheral thrombosis..... 884
- SPRAGUE, R. G. The use of mixtures of protamine zinc and regular insulin. 628
- SPRITZLER, R., E. CORDAY,—and M. PRINZMETAL. Studies on the coronary circulation. VII. The remarkable reserve power of the heart..... 450
- SPRITZLER, R., M. PRINZMETAL, L. L. SCHWARTZ, E. CORDAY,—H. C. BERGMAN and H. E. KRUGER. Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion..... 429
- STARRS, R. A. Subacute bacterial endocarditis presenting as a subarachnoid hemorrhage (report of a case with recovery). *Case Rep.*..... 139
- STECHER, R. M., A. H. HERSH and W. M. SOLOMON. The heredity of gout and its relationship to familial hyperuricemia..... 595
- SWIFT, H. F. The etiology of rheumatic fever..... 715
- TALBOTT, J. H. The diversity of gouty arthritis and its complications. 555
- THIMANN, K. V., G. PINCUS and—, Editors. The hormones: physiology, chemistry and applications. *Rev.*... 169
- THOMAS, E. W. Syphilis: its course and management. *Rev.*..... 361
- THOMPSON, C. E. and M. L. RICE, JR. Secondary amyloidosis in spinal cord injury..... 1057
- THOMPSON, S. A. and M. J. RAISBECK. The surgical rehabilitation of the coronary cripple..... 1010
- THOMSON, C., E. R. H. KURZ, E. L. CREHAN and—. Salmonella endocarditis with streptomycin failure. *Case Rep.*..... 497
- TRUMPER, M., A. CANTAROW and—. Clinical biochemistry. *Rev.*..... 934
- TUFT, L. Clinical allergy. *Rev.*..... 703
- UHR, N. and J. CHURG. Hypertrophic osteoarthropathy; report of a case associated with a chordoma of the base of the skull and lymphangitic pulmonary metastases. *Case Rep.*... 681
- VILTER, R. W., D. C. MITCHELL,—and C. F. VILTER. Hypersensitivity to folic acid. *Case Rep.*..... 1102
- WAKERLIN, G. E. Recent advances in the pathogenesis and treatment of essential hypertension..... 312
- WALKER, W. J., R. S. WALLERSTEIN and—. Hepatosplenomegaly and liver damage in Graves' disease. *Case Rep.*..... 904
- WALLACE, L. and E. CLARK. Electrocardiographic changes in a case of Wernicke's syndrome. *Case Rep.*... 675
- WALLERSTEIN, R. S. and W. J. WALKER. Hepatosplenomegaly and liver damage in Graves' disease. *Case Rep.*... 904
- WATSON, C. J. The prognosis and treatment of hepatic insufficiency.... 405
- WEINER, D., K. LANGE, and M. M. A. GOLD. Studies on the mechanism of cardiac injury in experimental hypothermia..... 989
- WEINER, M., J. M. SPITZER, N. ROSENTHAL,—and S. SHAPIRO. Pulmonary embolism: its incidence at necropsy in relation to peripheral thrombosis..... 884
- WEISS, E. and O. S. ENGLISH. Psychosomatic medicine: the clinical application of psychopathology to general medical problems. *Rev.*..... 532

- WELLS, E. B., M. FINLAND, H. S. COLLINS, T. M. GOCKE and—. Present status of aureomycin therapy 39
- WHIPPLE, A. O. An evaluation of radical surgery for carcinoma of the pancreas and ampullary region..... 624
- WHITE, P. D. and C. FERRERO. Research problems in coronary heart disease..... 33
- WHITE, P. D., F. E. GARDNER and—. Coronary occlusion and myocardial infarction associated with chronic rheumatic heart disease..... 1003
- WHITE, P. D., J. H. CURRENS and—. Great reduction in heart size attending the clearing of congestive heart failure in a man with hypertensive and coronary heart disease. *Case Rep.*..... 912
- WINSOR, T., G. E. BURCH and—. A primer of electrocardiography. *Rev.* 171
- WOLF, S. Summary of evidence relating life situation and emotional response to peptic ulcer..... 637
- WONG, Y. T., H. PACKER and—. Penicillin and penicillin-malaria in the treatment of tabes dorsalis..... 96
- WOODWARD, T. E. Chloromycetin and aureomycin: therapeutic results.. 53
- YATER, W. M. Fundamentals of internal medicine. *Rev.*..... 359
- ZHEUTLIN, B. Endocarditis caused by organism morphologically identified as *C. diphtheriae*. *Case Rep.*..... 339
- ZIMMERMAN, I. and N. MANN. Boeck's sarcoid: a case of sarcoidosis complicated by pulmonary emphysema and cor pulmonale. *Case Rep.*..... 153

# ANNALS OF INTERNAL MEDICINE

## SUBJECT INDEX

Volume 31, July-December, 1949

- A**DRENAL cortical function and pituitary-adrenal relationships, Some aspects of—. *Edit.*..... 925
- Aerosol and intratracheal penicillin. Pharmacodynamics of pulmonary absorption in man. I.—. E. A. GAENSLER, J. F. BEAKEY and M. S. SEGAL..... 582
- II. The Influence of various diluents on aerosol and intratracheal penicillin. J. F. BEAKEY, E. A. GAENSLER and M. S. SEGAL..... 805
- Aerosol penicillin in allergic patients with respiratory infections. M. A. GREEN..... 260
- Allergy, Clinical—. L. TUFT. *Rev.*... 703
- Allergy factor in disease, The—. R. A. COOKE..... 17
- Aminopterin in the treatment of acute leukemia. *Edit.*..... 1129
- Amyloidosis, Secondary—. D. C. DAHLIN..... 105
- Amyloidosis, Secondary—in spinal cord injury. C. E. THOMPSON and M. L. RICE, JR..... 1057
- Analgesia and anesthesia, Obstetric—. F. F. SNYDER. *Rev.*..... 705
- Anginal syndrome during sodium succinate therapy. C. S. DWYER, S. KRONENBERG and M. SAKLAD. *Case Rep.*..... 148
- Arthritis and allied conditions. B. I. COMROE. *Rev.*..... 932
- Arthritis, gouty—, The diversity of—and its complications. J. H. TALBOTT..... 555
- Atabrine toxicity, Clinical observations on atypical lichen planus and related dermatoses presumably due to—. A. FEDER..... 1078
- Aureomycin, Chloromycetin and—: therapeutic results. T. E. WOODWARD..... 53
- Aureomycin. *Edit.*..... 163
- Aureomycin in acute infectious mononucleosis. B. J. GRUSKIN. *Case Rep.*... 678
- Aureomycin therapy, Present status of —. M. FINLAND, H. S. COLLINS, T. M. GOCKE and E. B. WELLS..... 39
- Auscultation, Clinical—of the heart. S. A. LEVINE and W. P. HARVEY. *Rev.*..... 704
- B**AL (British Anti-Lewisite), The use of—in the treatment of the injurious effects of arsenic, mercury, and other metallic poisons. W. T. LONGCOPE and J. A. LUETSCHER, JR.. 545
- Barbiturate poisoning in man, Sodium succinate—an analeptic for—. R. H. BARRETT..... 739
- Bile ducts, Diseases of the liver, gallbladder, and—. S. S. LICHTMAN. *Rev.*..... 531
- Biochemistry, Clinical—. A. CANTAROW and M. TRUMPER. *Rev.*..... 934
- Biochemistry, Human—. I. S. KLEINER. *Rev.*..... 1134
- Blastomycosis, Immunologic types of —: a report of 40 cases. D. T. SMITH 463
- Boeck's sarcoid: a case of sarcoidosis complicated by pulmonary emphysema and cor pulmonale. I. ZIMMERMAN and N. MANN. *Case Rep.*... 153
- C**ALCAREOUS pancreatitis. C. A. DOMZALSKI, JR..... 650
- Cancer diagnosis, A survey of the actualities and potentialities of exfoliative cytology in—. G. N. PAPANICOLAOU 661
- Cancer of the lung, Superior vena cava obstruction in primary—. S. E. ROSENBLUM..... 470
- Carcinoma, metastatic—, Paraplegia secondary to—treated with stilbestrol. I. S. EDELMAN. *Case Rep.*... 1098
- Carcinoma of the pancreas and ampullary region, An evaluation of radical surgery for—. A. O. WHIPPLE..... 624
- Cardiac injury in experimental hypothermia, Studies on the mechanism of—. K. LANGF, D. WEINER and M. M. A. GOLD..... 989

- Cardiology. W. EVANS. *Rev.*..... 172
- Cardiovascular disease. L. H. SIGLER.  
*Rev.*..... 934
- Cardiovascular diseases, A physiologic  
and clinical study of —. Heart:—  
A. A. LUISADA. *Rev.*..... 1133
- Case studies in the psychopathology  
of crime. B. KARPMAN. *Rev.*..... 170
- C. diphtheriae*, Endocarditis caused by  
organism morphologically and cultur-  
ally identified as—. B. ZHEUTLIN.  
*Case Rep.*..... 339
- Chest x-ray surveys in general hospitals,  
a critical review. K. R. BOUCOT,  
D. A. COOPER, E. W. MARSHALL and  
F. MACD. RICHARDSON..... 889
- Child psychiatry. L. KANNER. *Rev.*... 362
- Chloromycetin and aureomycin: thera-  
peutic results. T. E. WOODWARD.... 53
- Chordoma of the base of the skull, Re-  
port of a case associated with a—and  
lymphangitic pulmonary metastases.  
Hypertrophic osteoarthropathy;—  
N. UHR and J. CHURG. *Case Rep.*... 681
- Circulation, Studies on the coronary—  
VI. Loss of myocardial contractility  
after coronary artery occlusion. M.  
PRINZMETAL, L. E. SCHWARTZ, E.  
CORDAY, R. SPRITZLER, H. C. BERG-  
MAN and H. E. KRUGER..... 429
- VII. The remarkable reserve power  
of the heart. E. CORDAY, R. SPRITZ-  
LER and M. PRINZMETAL..... 450
- Cirrhosis, The incidence of hypertension  
in portal—: a study of 80 necropsied  
cases of portal cirrhosis. S. D.  
SPATT and P. ROSENBLATT..... 479
- Clinical allergy. L. TUFT. *Rev.*..... 703
- Clinical biochemistry. A. CANTAROW  
and M. TRUMPER. *Rev.*..... 934
- Clinical entity, On the—. O. E.  
GUTTENTAG..... 484
- Clinical manifestations and laboratory  
diagnosis of rickettsialpox, The—  
H. M. ROSE..... 871
- Clinical observations on atypical lichen  
planus and related dermatoses pre-  
sumably due to atabrine toxicity. A.  
FEDER..... 1078
- Colitis, Nitrogen metabolism in chronic  
idiopathic ulcerative—and its thera-  
peutic significance. T. S. SAPPING-  
TON and H. L. BOCKUS..... 282
- Conditioned reflexes and neuron organ-  
ization. J. KONORSKI. *Rev.*..... 1133
- Coronary artery disease, A complica-  
tion of—. The shoulder-hand syn-  
drome;—. A. W. HILKER..... 303
- Coronary artery disease. E. P. BOAS  
and N. F. BOAS. *Rev.*..... 360
- Coronary circulation, Studies on the—  
VI. Loss of myocardial contractility  
after coronary artery occlusion. M.  
PRINZMETAL, L. E. SCHWARTZ, E.  
CORDAY, R. SPRITZLER, H. C. BERG-  
MAN and H. E. KRUGER..... 429
- VII. The remarkable reserve power  
of the heart. E. CORDAY, R. SPRITZ-  
LER and M. PRINZMETAL..... 450
- Coronary cripple, The surgical rehabili-  
tation of the—. S. A. THOMPSON  
and M. J. RAISBECK..... 1010
- Coronary heart disease, Research prob-  
lems in—. P. D. WHITE and C.  
FERRERO..... 33
- Coronary occlusion and myocardial  
infarction associated with chronic  
rheumatic heart disease. F. E.  
GARDNER and P. D. WHITE..... 1003
- Crime, Case studies in the psychopath-  
ology of—. B. KARPMAN. *Rev.*.... 170
- Curare (d-tubocurarine in oil and wax),  
The Use of—in the treatment of  
muscle spasm in rheumatic disorders.  
H. M. MARGOLIS and P. S. CAPLAN... 615
- Cysts, splenic—, Diagnostic features of  
—with case report and review of the  
literature. A. A. FISCHL and J.  
PAPPS. *Case Rep.*..... 1105
- Cytology, exfoliative—in cancer diag-  
nosis, A survey of the actualities and  
potentialities of—. G. N. PAPANI-  
COLAOU..... 661
- D**EATH due to parathion, an anti-  
cholinesterase insecticide. D.  
GROB, W. L. GARLICK, G. G. MER-  
RILL and H. C. FREIMUTH. *Case  
Rep.*..... 899
- Dermatoses, Clinical observations on  
atypical lichen planus and related—  
presumably due to atabrine toxicity.  
A. FEDER..... 1078
- Diagnosis of pneumonia preceding tu-  
berculosis, The—. A. S. HARTZ..... 1066

- Diagnostic features of splenic cysts with case report and review of the literature. A. A. FISCHL and J. PAPPS. *Case Rep.*..... 1105
- Diseases of the liver, gallbladder and bile ducts. S. S. LICHTMAN. *Rev.*... 531
- E**LECTROCARDIOGRAM in old age, On the significance of the normal—. T. T. FOX..... 120
- Electrocardiographic changes in a case of Wernicke's syndrome. L. WALLACE and E. CLARK. *Case Rep.*..... 675
- Electrocardiographic syndrome following paroxysmal tachycardia, The—. J. G. SMITH. *Case Rep.*..... 504
- Electrocardiography, An atlas of—. W. DRESSLER and H. ROESLER. *Rev.*..... 933
- Electrocardiography, A primer of—. G. E. BURCH and T. WINSOR. *Rev.*... 171
- Electrocardiography*. Unipolar extremity leads in records with large Q<sub>s</sub>. H. J. LOWEN and H. E. B. PARDEE... 456
- Electroencephalogram, The—. *Edit.*... 698
- Electrokymography of the heart and great vessels: principles and application. B. R. BOONE, G. F. ELLINGER and F. G. GILICK..... 1030
- Electron microscopy in relation to the medical sciences. S. MUDD..... 570
- Embolism, Pulmonary—: its incidence at necropsy in relation to peripheral thrombosis. J. M. SPITZER, N. ROSENTHAL, M. WEINER and S. SHAPIRO..... 884
- Embolism, Pulmonary—with acute cor pulmonale and extremely rapid ventricular rate in a young, active, apparently healthy adult. W. F. RENNER. *Case Rep.*..... 1090
- Emotional factors in organic disease. W. C. MENNINGER..... 207
- Empyema, Putrid—with a bronchopleural fistula successfully treated with penicillin. A. L. FORSGREN. *Case Rep.*..... 691
- Endocarditis caused by organism morphologically and culturally identified as *C. diphtheriae*. B. ZHEUTLIN. *Case Rep.*..... 339
- Endocarditis lenta, Streptomycin therapy of *Hemophilus influenzae*—. W. S. MIDDLETON. *Case Rep.*..... 511
- Endocarditis, Salmonella—with streptomycin failure. E. R. H. KURZ, E. L. CREHAN and C. THOMSON. *Case Rep.*..... 497
- Endocarditis, Subacute bacterial—presenting as a subarachnoid hemorrhage (report of a case with recovery). R. A. STARRS. *Case Rep.*..... 139
- Eosinophilia, Tropical—with report of a case treated with penicillin. P. H. MORTON and C. C. JONES. *Case Rep.*..... 1112
- Erythema multiforme bullosum due to sulfadiazine sensitivity controlled with procaine intravenously. E. APPELBAUM and S. M. ARONSON. *Case Rep.*..... 146
- Esophageal varices, The surgical treatment of bleeding—by portal systemic venous shunts with a report of 34 cases. R. R. LINTON..... 794
- Etiology and management of the hemorrhagic diatheses, The—. C. A. DOAN..... 967
- Etymology, Medical—, the history and derivation of medical terms for students of medicine, dentistry and nursing. O. H. P. PEPPER. *Rev.*..... 530
- F**EVER, Immunologic studies in rheumatic—. *Edit.*..... 354
- Fever, The etiology of rheumatic—. H. F. SWIFT..... 715
- Fever, Typhoid and paratyphoid—in immunized subjects. A. H. ROSENBLUM..... 235
- Fluorosis, Industrial—: a study of the hazard to man and animals near Fort William, Scotland. *Rev.*..... 361
- Folic acid, Hypersensitivity to—. D. C. MITCHELL, R. W. VILTER and C. F. VILTER. *Case Rep.*..... 1102
- Fundamentals of internal medicine. W. M. YATER. *Rev.*..... 359
- Fundamentals, The—of pulmonary tuberculosis and its complications, for the student, the teacher, and the practicing physician. E. W. HAYFS, Editor. *Rev.*..... 532
- G**ALLBLADDER and bile ducts, Diseases of the liver,—. S. S. LICHTMAN. *Rev.*..... 531

- Gastric mucosa, Prolapsed—: a possible cause of "gastric" symptoms in right heart failure. M. MELAMED and A. MELAMED..... 245
- Gastritis, Pancreatic lithiasis and— (cases with gastroscopic observations). M. M. MOURAO and R. SCHINDLER..... 83
- Gout, The heredity of—and its relationship to familial hyperuricemia. R. M. STECHER, A. H. HERSH and W. M. SOLOMON..... 595
- Gouty arthritis and its complications, The diversity of—. J. H. TALBOTT.. 555
- Graves' disease, Hepatosplenomegaly and liver damage in—. R. S. WALLERSTEIN and W. J. WALKER. *Case Rep.*..... 904
- H** EART and great vessels, Electrokymography of the—: principles and application. B. R. BOONE, G. F. ELLINGER and F. G. GILICK..... 1030
- Heart and kidney disease, Treatment of—and of hypertensive and arteriosclerotic vascular disease with the rice diet. W. KEMPNER..... 821
- Heart: A physiologic and clinical study of cardiovascular diseases. A. A. LUISADA. *Rev.*..... 1133
- Heart, Clinical auscultation of the—. S. A. LEVINE and W. P. HARVEY. *Rev.*..... 704
- Heart disease, chronic rheumatic—, Coronary occlusion and myocardial infarction associated with—. F. E. GARDNER and P. D. WHITE..... 1003
- Heart disease, Research problems in coronary—. P. D. WHITE and C. FERRERO..... 33
- Heart failure, A possible cause of "gastric" symptoms in right—. Prolapsed gastric mucosa:—. M. MELAMED and A. MELAMED..... 245
- Heart failure, congestive, in a man with hypertensive and coronary heart disease, Great reduction in heart size attending the clearing of—. J. H. CURRENS and P. D. WHITE. *Case Rep.*..... 912
- Heart failure, New light on the pharmacodynamics of—. *Edit.*..... 524
- Hemophilus influenzae* endocarditis lenta, Streptomycin therapy of—. W. S. MIDDLETON. *Case Rep.*..... 511
- Hemorrhage, Subacute bacterial endocarditis presenting as a subarachnoid—(report of a case with recovery). R. A. STARRS. *Case Rep.*..... 139
- Hemorrhagic diatheses, The etiology and management of the—. C. A. DOAN..... 967
- Hepatic insufficiency, The prognosis and treatment of—. C. J. WATSON. 405
- Hepatitis, Viral—: problems and progress. J. R. NEEFE..... 857
- Hepatosplenomegaly and liver damage in Graves' disease. R. S. WALLERSTEIN and W. J. WALKER. *Case Rep.* 904
- Heredity of gout and its relationship to familial hyperuricemia, The—. R. M. STECHER, A. H. HERSH and W. M. SOLOMON..... 595
- Histoplasmosis, Stilbamidine in the treatment of—. J. H. SEABURY. *Case Rep.*..... 520
- Hormones, The—: physiology, chemistry and applications. G. PINCUS and K. V. THIMANN, Editors. *Rev.*... 169
- Hospital, The—as a center of preventive medicine. S. BAYNE-JONES..... 7
- Human biochemistry. I. S. KLEINER. *Rev.*..... 1134
- Hypersensitivity to folic acid. D. C. MITCHELL, R. W. VILTER and C. F. VILTER. *Case Rep.*..... 1102
- Hypertension in portal cirrhosis, The incidence of—: a study of 80 necropsied cases of portal cirrhosis. S. D. SPATT and P. ROSENBLATT..... 479
- Hypertension, Recent advances in the pathogenesis and treatment of essential—. G. E. WAKERLIN..... 312
- Hypertensive and arteriosclerotic vascular disease, Treatment of heart and kidney disease and of—with the rice diet. W. KEMPNER..... 821
- Hyperuricemia, The heredity of gout and its relationship to familial—. R. M. STECHER, A. H. HERSH and W. M. SOLOMON..... 595
- Hypothermia, Studies on the mechanism of cardiac injury in experimental—. K. LANGE, D. WEINER and M. M. A. GOLD..... 989

- I**LEITIS, Regional—. B. B. CROHN.  
*Rev.*..... 529
- Immunologic studies in rheumatic fever. *Edit.*..... 354
- Immunologic types of blastomycosis: a report of 40 cases. D. T. SMITH..... 463
- Industrial fluorosis: a study of the hazard to man and animals near Fort William, Scotland. *Rev.*..... 361
- Infarction, Myocardial—resulting in interventricular septal perforation: report of a case diagnosed during life. L. J. BICKERMAN and E. E. IRONS. *Case Rep.*..... 918
- Insulin, The use of mixtures of protamine zinc and regular—. R. G. SPRAGUE..... 628
- Internal medicine, Fundamentals of—. W. M. YATER. *Rev.*..... 359
- Internist, The—, past, present and future. W. W. PALMER..... 1
- K**APOSI'S sarcoma with secondary involvement of the jejunum, perforation and peritonitis. N. MITCHELL and I. A. FEDER. *Case Rep.*..... 324
- Kidney disease, Treatment of heart and—and of hypertensive and arteriosclerotic vascular disease with the rice diet. W. KEMPNER..... 821
- L**EUKEMIA, Aminopterin in the treatment of acute—. *Edit.*... 1129
- Lithiasis, Pancreatic—and gastritis (cases with gastroscopic observations). M. M. MOURAO and R. SCHINDLER..... 83
- Liver damage in Graves' disease, Hepatosplenomegaly and—. R. S. WALLERSTEIN and W. J. WALKER. *Case Rep.*..... 904
- Liver, gallbladder and bile ducts, Diseases of the—. S. S. LICHTMAN. *Rev.*..... 531
- Liver, Polycystic disease of the—; report of two cases diagnosed by peritoneoscopy. D. NIEMETZ, A. SOKOL and L. MEISTER. *Case Rep.*..... 319
- Lymphangitic pulmonary metastases, Report of a case associated with a chordoma of the base of the skull and—. Hypertrophic osteoarthropathy; —. N. UHR and J. CHURG. *Case Rep.*..... 681
- M**EDICAL Care, Newer concepts of—. R. P. McCOMBS..... 125
- Medical etymology, the history and derivation of medical terms for students of medicine, dentistry and nursing. O. H. P. PEPPER. *Rev.*..... 530
- Medicine, Textbook of—. J. CONYBEARE, Editor. *Rev.*..... 932
- Mental illness, Prefrontal operations for the treatment of—. J. L. POOL.... 424
- Mercurialism, Fatal—due to prolonged intravenous administration of a mercurial diuretic. M. B. SIEGEL and A. J. FRIEDMAN. *Case Rep.*..... 343
- Microscopy, Electron—in relation to the medical sciences. S. MUDD..... 570
- Mononucleosis, Aureomycin in acute infectious—. B. J. GRUSKIN. *Case Rep.*..... 678
- Myocardial infarction resulting in interventricular septal perforation: report of a case diagnosed during life. L. J. BICKERMAN and E. E. IRONS. *Case Rep.*..... 918
- N**ECROSIS of renal papillae. E. D. ROBBINS and A. ANGRIST..... 773
- Nephron, Lower—syndrome. G. E. BURCH and C. T. RAY..... 750
- Neuroanatomy, Correlative—. J. J. McDONALD, J. G. CHRUSID and J. LANGE. *Rev.*..... 704
- Neuron organization, Conditioned reflexes and—. J. KONORSKI. *Rev.*... 1133
- Nitrogen balance studies in chronic peptic ulcer disease. T. S. SAPPINGTON and H. L. BOCKUS..... 271
- Nitrogen metabolism in chronic idiopathic ulcerative colitis and its therapeutic significance. T. S. SAPPINGTON and H. L. BOCKUS..... 282
- O**BITUARIES
- Addis, Thomas..... 1155
- Alling, Frederic A..... 1157
- Anderson, Wilhelm S..... 963
- Ben-Asher, Solomon..... 184
- Blue, William Ramsey..... 962
- Cade, William Henry..... 1158
- Cook, George L..... 371
- Cullen, Victor Francis..... 543
- Douglas, Bruce Hutchinson..... 1155
- Elgart, Samuel..... 371

- George, Shaul..... 185  
 Gichner, Joseph Enoch..... 372  
 Graves, William Washington..... 962  
 Hall, Frederic W..... 372  
 Hargis, W. Huard, Jr..... 1157  
 Jack, Cecil McKee..... 964  
 Lewis, Thomas Krapfel..... 963  
 Litvak, Abraham M..... 186  
 Lockard, G. Carroll..... 964  
 Louria, Alexander L..... 543  
 Meehan, John William..... 544  
 Miller, Sydney R..... 183  
 Morgan, William Gerry..... 539  
 Muniz, Jorge Rodriguez..... 714  
 Pemberton, Ralph..... 543  
 Redwood, Frank Harrell..... 714  
 Reid, William Duncan..... 1155  
 Rudisill, Hillyer, Jr..... 1156  
 Rutledge, Clifford P..... 372  
 Simonds, Paul Edward..... 965  
 Skinner, George Alfred..... 544  
 Soley, Mayo Hamilton..... 541  
 Thomas, Anne Heath..... 186  
 Torbett, John Walter..... 1157  
 West, Randolph..... 184  
 Westmoreland, Robert Edward, Sr... 965  
 Westra, Jacob John..... 966  
 Obstetric analgesia and anesthesia.  
 F. F. SNYDER. *Rev.*..... 705  
 Organic disease, Emotional factors in—  
 W. C. MENNINGER..... 207  
 Osteoarthropathy, hypertrophic—; re-  
 port of a case associated with a chor-  
 doma of the base of the skull and  
 lymphangitic pulmonary metastases.  
 N. UHR and J. CHURG. *Case Rep.*... 681  
**P**ANCREATIC lithiasis and gastritis  
 (cases with gastroscopic observa-  
 tions). M. M. MOURAO and R.  
 SCHINDLER..... 83  
 Pancreatitis, Calcareous—. C. A.  
 DOMZALSKI, JR..... 650  
 Paraplegia secondary to metastatic  
 carcinoma treated with stilbestrol.  
 I. S. EDELMAN. *Case Rep.*..... 1098  
 Parathion, Death due to—, an anti-  
 cholinesterase insecticide. D. GROB,  
 W. L. GARLICK, G. G. MERRILL and  
 H. C. FREIMUTH. *Case Rep.*..... 899  
 Paratyphoid, Typhoid and—fever in  
 immunized subjects. A. H. ROSEN-  
 BLUM..... 235  
 Penicillin, Aerosol and intratracheal—.  
 Pharmacodynamics of pulmonary  
 absorption in man. I.—. E. A.  
 GAENSLER, J. F. BEAKEY and M. S.  
 SEGAL..... 582  
 II. The influence of various diluents  
 on aerosol and intratracheal peni-  
 cillin. J. F. BEAKEY, E. A. GAEN-  
 SLER and M. S. SEGAL..... 805  
 Penicillin, Aerosol—in allergic patients  
 with respiratory infections. M. A.  
 GREEN..... 260  
 Penicillin and penicillin-malaria in the  
 treatment of tabes dorsalis. H.  
 PACKER and Y. T. WONG..... 96  
 Penicillin, Putrid empyema with a  
 bronchopleural fistula successfully  
 treated with—. A. L. FORSGREN.  
*Case Rep.*..... 691  
 Penicillin, Tropical eosinophilia with  
 report of a case treated with—. P.  
 H. MORTON and C. C. JONES. *Case  
 Rep.*..... 1112  
 Peptic ulcer disease, Nitrogen balance  
 studies in chronic—. T. S. SAPPING-  
 TON and H. L. BOCKUS..... 271  
 Peptic ulcer, Summary of evidence re-  
 lating life situation and emotional  
 response to—. S. WOLF..... 637  
 Pharmacodynamics of heart failure,  
 New light on the—. *Edit.*..... 524  
 Pharmacodynamics of pulmonary ab-  
 sorption in man. I. Aerosol and  
 intratracheal penicillin. E. A. GAEN-  
 SLER, J. F. BEAKEY and M. S. SEGAL. 582  
 II. The influence of various diluents  
 on aerosol and intratracheal peni-  
 cillin. J. F. BEAKEY, E. A. GAEN-  
 SLER and M. S. SEGAL..... 805  
 Pheochromocytoma: diagnosis and  
 treatment. G. F. CAHILL and H.  
 ARANOW, JR..... 389  
 Phlebitis and the diagnosis of throm-  
 boangiitis obliterans. E. A. ED-  
 WARDS..... 1019  
 Pituitary-adrenal relationships, Some  
 aspects of adrenal cortical function  
 and—. *Edit.*..... 925  
 Pneumonia, The diagnosis of—preced-  
 ing tuberculosis. A. S. HARTZ..... 1066  
 Poisoning, barbiturate—in man,  
 Sodium succinate—an analeptic for  
 —. R. H. BARRETT..... 739



- Poisons, The use of BAL (British Anti-Lewisite) in the treatment of the injurious effects of arsenic, mercury and other metallic poisons. W. T. LONGCOPE and J. A. LUETSCHER, JR.. 545
- Polycystic disease of the liver; report of two cases diagnosed by peritoneoscopy. D. NIEMETZ, A. SOKOL and L. MEISTER. *Case Rep.*..... 319
- Prefrontal operations for the treatment of mental illness. J. L. POOL..... 424
- Preventive medicine, The hospital as a center of—. S. BAYNE-JONES..... 7
- Procaine, Erythema multiforme bullosum due to sulfadiazine sensitivity controlled with—intravenously. E. APPELBAUM and S. M. ARONSON. *Case Rep.*..... 146
- Prognosis and treatment of hepatic insufficiency, The—. C. J. WATSON. 405
- Prolapsed gastric mucosa: a possible cause of "gastric" symptoms in right heart failure. M. MELAMED and A. MELAMED..... 245
- Protamine zinc and regular insulin, The use of mixtures of—. R. C. SPRAGUE 628
- Psychiatry, Child—. L. KANNER. *Rev.*..... 362
- Psychological medicine, Modern practice in—. J. R. REES, Editor. *Rev.* 1133
- Psychological medicine, Modern trends in—. N. G. HARRIS, Editor. *Rev.*... 171
- Psychopathology of crime, Case studies in the—. B. KARPMAN. *Rev.*..... 170
- Psychosomatic medicine: the clinical application of psychopathology to general medical problems. E. WEISS and O. S. ENGLISH. *Rev.*..... 532
- Pulmonary absorption in man, Pharmacodynamics of—. I. Aerosol and intratracheal penicillin. E. A. GAENSLER, J. F. BEAKEY and M. S. SEGAL..... 582
- II. The influence of various diluents on aerosol and intratracheal penicillin. J. F. BEAKEY, E. A. GAENSLER and M. S. SEGAL..... 805
- Pulmonary disease manifestations of ankylosing spondylarthritis. K. A. HAMILTON..... 216
- Pulmonary embolism: its incidence at necropsy in relation to peripheral thrombosis. J. M. SPITZER, N. ROSENTHAL, M. WEINER and S. SHAPIRO..... 884
- Pulmonary embolism with acute cor pulmonale and extremely rapid ventricular rate in a young, active, apparently healthy adult. W. F. RENNER. *Case Rep.*..... 1090
- Pulmonary tuberculosis, The fundamentals of—and its complications, for the student, the teacher, and the practicing physician. E. W. HAYES, Editor. *Rev.*..... 532
- R**ED blood cell sensitivity in Caucasians. P. M. NEUDA..... 1024
- Reduction, Great—in heart size attending the clearing of congestive heart failure in a man with hypertensive and coronary heart disease. J. H. CURRENS and P. D. WHITE. *Case Rep.*..... 912
- Reflexes, Conditioned—and neuron organization. J. KONORSKI. *Rev.*.... 1133
- Regional ileitis. B. B. CROHN. *Rev.*... 529
- Renal papillae, Necrosis of—. E. D. ROBBINS and A. ANGRIST..... 773
- Research problems in coronary heart disease. P. D. WHITE and C. FERRERO..... 33
- Respiratory infections, Aerosol penicillin in allergic patients with —. M. A. GREEN..... 260
- Rheumatic disorders, The use of curare (d-tubocurarine in oil and wax) in the treatment of muscle spasm in—. H. M. MARGOLIS and P. S. CAPLAN.. 615
- Rheumatic fever, Immunologic studies in—. *Edil.*..... 354
- Rheumatic fever, The etiology of—. H. F. SWIFT..... 715
- Rheumatic heart disease, Coronary occlusion and myocardial infarction associated with chronic—. F. E. GARDNER and P. D. WHITE..... 1003
- Rice diet, Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the—. W. KEMPNER..... 821
- Rickettsialpox, The clinical manifestations and laboratory diagnosis of—. H. M. ROSE..... 871

- S**ALMONELLA endocarditis with streptomycin failure. E. R. H. KURZ, E. L. CREHAN and C. THOMSON. *Case Rep.*..... 497
- Sarcoid, Boeck's—: a case of sarcoidosis complicated by pulmonary emphysema and cor pulmonale. I. ZIMMERMAN and N. MANN. *Case Rep.* 153
- Sarcoma, Kaposi's—with secondary involvement of the jejunum, perforation and peritonitis. N. MITCHELL and I. A. FEDER. *Case Rep.*... 324
- Shoulder-hand syndrome, The—: a complication of coronary artery disease. A. W. HILKER..... 303
- Sodium succinate—an analeptic for barbiturate poisoning in man. R. H. BARRETT..... 739
- Sodium succinate therapy, Anginal syndrome during—. C. S. DWYER, S. KRONENBERG and M. SAKLAD. *Case Rep.*..... 148
- Sound.* Xiphosternal crunch: an analysis of 106 cases among 3,224 army separatees. I. SCHWAB, G. L. SMILEY and W. P. MEYN..... 228
- Spinal cord injury, Secondary amyloidosis in—. C. E. THOMPSON and M. L. RICE, JR..... 1057
- Splenic cysts, Diagnostic features of—with case report and review of the literature. A. A. FISCHL and J. PAPPS. *Case Rep.*..... 1105
- Spondylarthritis, Pulmonary disease manifestations of ankylosing—. K. A. HAMILTON..... 216
- Stilbamidine in the treatment of histoplasmosis. J. H. SEABURY. *Case Rep.*..... 520
- Stilbestrol, Paraplegia secondary to metastatic carcinoma treated with—. I. S. EDELMAN. *Case Rep.*..... 1098
- Streptomycin failure, Salmonella endocarditis with—. E. R. H. KURZ, E. L. CREHAN and C. THOMSON. *Case Rep.*..... 497
- Streptomycin therapy of *Hemophilus influenzae* endocarditis lenta. W. S. MIDDLETON. *Case Rep.*..... 511
- Studies on the mechanism of cardiac injury in experimental hypothermia. K. LANGE, D. WEINER and M. M. A. GOLD..... 989
- Studies on the coronary circulation. VI. Loss of myocardial contractility after coronary artery occlusion. M. PRINZMETAL, L. E. SCHWARTZ, E. CORDAY, R. SPRITZLER, H. C. BERGMAN and H. E. KRUGER..... 429
- VII. The remarkable reserve power of the heart. E. CORDAY, R. SPRITZLER and M. PRINZMETAL..... 450
- Sulfadiazine sensitivity, Erythema multiforme bullosum due to—controlled with procaine intravenously. E. APPELBAUM and S. M. ARONSON. *Case Rep.*..... 146
- Summary of evidence relating life situation and emotional response to peptic ulcer. S. WOLF..... 637
- Surgery, radical—for carcinoma of the pancreas and ampullary region, An evaluation of—. A. O. WHIPPLE.... 624
- Surgical rehabilitation of the coronary cripple, The—. S. A. THOMPSON and M. J. RAISBECK..... 1010
- Surgical treatment of bleeding esophageal varices by portal systemic venous shunts with a report of 34 cases, The—. R. R. LINTON..... 794
- Survey of the actualities and potentialities of exfoliative cytology in cancer diagnosis, A—. G. N. PAPANICOLAOU..... 661
- Syphilis: its course and management. E. W. THOMAS. *Rev.*..... 361
- T**ABES dorsalis, Penicillin and penicillin-malaria in the treatment of—. H. PACKER and Y. T. WONG.... 96
- Tachycardia, Persistent—caused by snake venom. W. H. GLASS. *Case Rep.*..... 517
- Tachycardia, The electrocardiographic syndrome following paroxysmal—. J. G. SMITH. *Case Rep.*..... 504
- Thromboangiitis obliterans, Phlebitis and the diagnosis of—. E. A. EDWARDS..... 1019
- Thrombosis, A case of mesenteric venous—with survival. A. M. GOLDMAN and J. D. RIVES. *Case Rep.*..... 329
- Thrombosis. Pulmonary embolism: its incidence at necropsy in relation to

- peripheral thrombosis. J. M. SPITZER, N. ROSENTHAL, M. WEINER and S. SHAPIRO..... 884
- Thrombosis, Vena cava—with polycythemia and leg ulcer. J. A. BOONE and H. G. SMITHY. *Case Rep.*..... 513
- Treatment of heart and kidney disease and of hypertensive and arteriosclerotic vascular disease with the rice diet. W. KEMPNER..... 821
- Tropical eosinophilia with report of a case treated with penicillin. P. H. MORTON and C. C. JONES. *Case Rep.*..... 1112
- Tuberculosis in childhood. D. S. PRICE. *Rev.*..... 171
- Tuberculosis, The diagnosis of pneumonia preceding—. A. S. HARTZ.... 1066
- Tuberculosis, The fundamentals of pulmonary—and its complications, for the student, the teacher, and the practicing physician. E. W. HAYES, Editor. *Rev.*..... 532
- Typhoid and paratyphoid fever in immunized subjects. A. H. ROSENBLUM..... 235
- ULCER, peptic—, Summary of evidence relating life situation and emotional response to—. S. WOLF.. 637
- Unipolar extremity leads in records with large Qs. H. J. LOWEN and H. E. B. PARDEE.....
- VASCULAR disease, Treatment of heart and kidney disease and of hypertensive and arteriosclerotic—with the rice diet. W. KEMPNER....
- Vena cava obstruction, Superior—in primary cancer of the lung. S. E. ROSENBLUM.....
- Vena cava thrombosis with polycythemia and leg ulcer. J. A. BOONE and H. G. SMITHY. *Case Rep.*.....
- Viral hepatitis: problems and progress. J. R. NEEFE.....
- WERNICKE'S syndrome, Electrocardiographic changes in a case of—. L. WALLACE and E. CLARK. *Case Rep.*.....
- XIPHOSTERNAL crunch: an analysis of 106 cases among 3,224 army separatees. L. SCHWAB, G. L. SMILEY and W. P. MEYN.....
- X-ray surveys, Chest—in general hospitals, a critical review. K. R. BOUCOT, D. A. COOPER, E. W. MARSHALL and F. MACD. RICHARDSON.....

